Risk Factors of Long-Term Graft Loss in Renal Transplant Recipients with Chronic Allograft Dysfunction

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Abstract

Background: **Graft loss owing to chronic allograft dysfunction is a major concern in renal transplant recipients. We assessed the affect of immune and nonimmune risk factors on death-censored graft loss in renal transplant recipients with chronic allograft dysfunction.**

Materials and Methods: **We performed a retrospective, single-center study on 214 renal transplant recipients with chronic allograft dysfunction among 1534 renal transplant recipients at the Urmia University Hospital from 1997 to 2005. Data registry includes details from all renal transplants. The renal transplant recipient information is regularly updated to determine current graft function, graft loss, or renal transplant recipient's death. The selection criteria were a functional renal allograft for at least 1 year and a progressive decline in allograft function.**

Results: **Increasing donor age (RR=1.066; *P* < .001), recipient age (RR=1.021, *P* = .0), recipient weight (RR=1.024; *P* = .029), and waiting time on dialysis to transplant. (RR=1.047; *P* = .006), pretransplant hypertension (RR=3.126; *P* < .001), pretransplant diabetes (RR=5.787; *P* < .001), delayed graft function (RR=6.087; *P* < .001), proteinuria (RR=2.663; *P* = .001), posttransplant diabetes (RR=2.285; *P* = .015), posttransplant hypertension (RR=2.047; *P* = .017), and AR (RR=3.125; *P* < .001). Patients in stage 2 at the beginning of chronic allograft dysfunction relative to stage 1 (RR=4.823; *P* < .001) and patients in stage 3 at the beginning of chronic allograft dysfunction relative to stage 1 (RR=123.06; *P* < .001) were significant risk factors for death-censored graft loss. Using mycophenolate mofetil versus azathioprine reduced death-censored graft loss (RR=0.499; *P* ≤ .001).**

Conclusion: **We found that age of donor, pretransplant hypertension, pretransplant diabetes, type of immunosuppression (mycophenolate mofetil vs azathioprine), delayed graft function, proteinuria, and stage of allograft dysfunction at the start of chronic allograft dysfunction are the major risk factors for late renal allograft dysfunction.**

Key words: *Renal transplantation, Survival, Chronic allograft dysfunction*

Introduction

Globally, more than 500 million individuals, or about 1 adult in 10 in the general population, have some form of chronic kidney disease. Worldwide, over 1.5 million people are currently alive either through dialysis or transplant. The cumulative global cost for renal replacement therapy is predicted to exceed USD $1 trillion (1). In addition to its costs, chronic kidney disease leads to significant 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 estimations, long-term outcomes have not significantly improved in these patients (5-8). Graft loss due to chronic allograft dysfunction is a major concern in renal transplant recipients (9, 10). Clinically chronic allograft dysfunction is commonly characterized by a progressive decline in glomerular filtration rate over time (11).

Multiple factors have been implicated in the pathogenesis of chronic allograft dysfunction both

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immune and nonimmune factors. This study sought to assess the affect of immune and nonimmune risk factors in death-censored graft loss in renal transplant recipients with chronic allograft dysfunction using multivariate analysis.

Materials and Methods

We performed a retrospective single-center study on 214 renal transplant recipients with chronic allograft dysfunction among 1534 renal transplant recipients at the Urmia University Hospital from 1997 to 2005. Data registry includes details from all renal transplants carried out at Urmia University Hospital. The patients' information is regularly updated to determine current graft function, graft loss, or patient death. The selection criteria were a functional renal allograft for at least 1 year and a progressive decline in allograft function.

Risk factors were collected on donor, recipient, and transplant characteristics that have previously been reported to influence graft survival. We assessed the role of prognostic factors including donors and recipients age (y), weight of recipients, and dialysis before transplant as continuous variables, pretransplant hypertension, (hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg, diastolic blood pressure of ≥ 90 mm Hg, or the use of any antihypertensive drug), pretransplant diabetes (need for 1 or more drugs) as categoric variables. After transplant, the following variables were considered: type of immunosuppression (cyclosporine plus mycophenolate mofetil vs cyclosporine plus azathioprine), delayed graft function, proteinuria, posttransplant diabetes mellitus, posttransplant hypertension, acute rejection episodes, and glomerular filtration rate at the beginning of chronic allograft dysfunction process as categoric variables. Delayed graft function was defined as the need of 1 or more dialysis sessions after transplant. Acute rejection was defined by the need for treatment, with or without biopsy confirmation. Death-censored graft loss was defined by return to dialysis or retransplant.

We recorded serum creatinine at each visit until graft failure or last follow-up and used them to estimate the glomerular filtration rate). The Cockcroft-Gault estimation of creatinine clearance (CLcr)=[(140 _ age in years) × (weight in kilograms)] ÷ (72 × serum creatinine mL/min) × 0.85 (if female) was used to estimate kidney function (12). We hypothesized that National Kidney Fundation and Kidney Disease Outcome Quality Initiative K/DOQI classification of chronic kidney disease is applicable to determine graft function in renal transplant recipients (13).

Statistical analysis was performed as follows. First, we assessed the risk factors for death-censored graft loss by univariate analysis. Then, we used the multivariate Cox regression to assess main effect of each risk factor. The best model selected with stepwise method with PE=0.2 and PR=0.15. The Kaplan-Meier survivor function was used to estimate death-censored graft survival curve. Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 16.0, SSPS Inc, Chicago, IL, USA). All reported significance levels are from 2-tailed tests.

Results

Among 1534 renal transplant recipients, 214 patients fulfilled chronic allograft dysfunction criteria. Among patients with chronic allograft dysfunction, 152 were male (71%) and 62 were female (29%). Mean time to enter to chronic allograft dysfunction stage 1 was 9.8 ± 2.4 months posttransplant. Mean of creatinine clearance (CLcr) measurement during follow-up was 32.1 ± 9.9 times (range, 12-56 times). Mean age of donors and recipients were 30.4 and 38.8 years. Descriptive statistics in renal transplant recipients were mean weights 70.4 kg, waiting time on dialysis was 14.9 months, pretransplant hypertension in 61 (28.5%), pretransplant diabetes mellitus in 45 (21%), using cyclosporine and mycophenolate mofetil in 98 (45.8%), delayed graft function occurred in 16 (7.7%), proteinuria in 114 (53.3%), posttransplant diabetes mellitus in 27 (12.6%), posttransplant hypertension in 124 (57.9%), and acute rejection in 52 (24.3%). At the beginning of the study, 117 patients (54.7%) belonged to stage 1, 81 (37.9%) to stage 2, 16 (7.5%) to stage 3, and no one to stage 4 or 5. At the end of study, no patients belonged to stage 1, 22 to stage 2 (10.3%), 85 to stage 3 (39.7%), 50 to stage 4 (23.4%), and 57 to stage 5 (26.6%). The characteristics of the renal transplant recipient's population are displayed in the first columns of Table 1.

The unadjusted death-censored graft loss was 26.6%. The death-censored graft survival curve estimated using Kaplan-Meier method is shown in Figure 1a.

Table 1. Variables associated with death-censored graft loss in univariate and multivariate Cox regression with stepwise selection method.

Variables	Mean ± SE (%)	Univariate			Multivariate		
		β	*P* value	RR	β	*P* value	RR
Donor age (y)	30.4 ± 0.47	0.064	< .001	1.066	0.057	.003	1.058
Recipient age (y)	38.8 ± 0.92	0.020	.047	1.021	-	-	-
Recipient weight (kg)	70.4 ± 0.91	0.024	.029	1.024	-	-	-
Waiting time on dialysis to transplant (mo)	14.9 ± 0.51	0.046	.006	1.047	-	-	-
Pretransplant hypertension (yes vs no)	61 (28.5%)	0.717	.017	2.047	-	-	-
Pretransplant diabetes (yes vs no)	45 (21%)	1.756	< .001	5.787	1.465	< .001	4.329
Type of immunosuppression (CsA & MMF vs CsA & AZA)	98 (45.8%)	-0.695	.017	0.499	-0.391	.052	0.676
DGF (yes vs no)	16 (7.5%)	1.806	< .001	6.087	0.716	.081	2.046
Proteinuria (yes vs no)	114 (53.3%)	0.979	.001	2.663	0.672	.033	1.959
Posttransplant diabetes (yes vs no)	27 (12.6%)	0.826	.015	2.285	-	-	-
Posttransplant hypertension (yes vs no)	124 (57.9%)	1.231	< .001	3.126	0.477	.071	1.611
AR (yes vs no)	52 (24.3%)	1.139	< .001	3.125	-	-	-
Stage of GFR in start of CAD	81 (37.9%)	1.573	< .001	4.823	1.129	.001	3.092
2 vs 1	16 (7.5%)	4.813	< .001	123.06	4.457	< .001	86.22
3 vs 1							

Abbreviations: AR, acute rejection; AZA, azathioprine; CAD, coronary artery disease; CsA, cyclosporine; DGF, delayed graft function; GFR, glomerular filtration rate; MMF, mycophenolate mofetil

The main purpose of this study was to determine the best model for prognoses of long-term graft survival in renal transplant recipients with chronic allograft dysfunction. We assessed each of variables with the univariate Cox proportional hazard model. Increasing donor age (RR=1.066; $P < .001$), recipient age (RR=1.021; $P = .047$), recipient weight (RR=1.024; $P = .029$), waiting time on dialysis to transplant (RR=1.047; $P = .006$), pretransplant hypertension (RR=3.126; $P < .001$), pretransplant diabetes (RR=5.787; $P < .001$), delayed graft function (RR=6.087; $P < .001$), proteinuria (RR=2.663; $P = .001$), posttransplant diabetes (RR=2.285; $P = .015$), posttransplant hypertension (RR=2.047; $P = .017$), acute rejection (RR=3.125; $P < .001$), patients in stage 2 at the beginning of chronic allograft dysfunction relative to stage 1 (RR=4.823; $P < .001$), and patients in stage 3 at the beginning of chronic allograft dysfunction relative to stage 1 (RR=123.06; $P < .001$) were significant risk factors for death-censored graft loss after renal transplant. Using cyclosporine plus mycophenolate mofetil versus cyclosporine plus azathioprine decreased death-censored graft loss (RR=0.499; $P \leq .001$) (Table 1).

There was strong colinearity between risks factors; therefore, adjusted death-censored graft loss assessed with the multivariate Cox proportional hazard regression. The best model selected with stepwise method with PE=0.2 and PR=0.15. The significant prognostic factors are shown in Table 1. The results show that donor age was a significant prognostic factor for death-censored graft loss, with increasing 1 year in donor age, relative risk for death-censored graft loss was increase 1.058 ($P < .001$). Posttransplant hypertension conferred a 61% increased risk for death-censored graft loss. Pretransplant diabetes remained a significant risk factor (RR=4.329) for death-censored graft loss ($P < .001$) (Figure 1d). Another significant risk factor for death-censored graft loss was delayed graft function. Risk of death-censored graft loss in patients with delayed graft function was 2.046 times relative to whom without delayed graft function ($P = .081$) (Figure 1f). Patients with proteinuria had increased risk of death-censored graft loss, RR=1.959, relative to whom without proteinuria ($P = .033$) (Figure 1).

The results of the Cox proportional hazard regression shown that risk of death-censored graft loss in patients on stage 2 at the beginning of chronic allograft dysfunction relative to stage 1 significantly increased (RR=3.092, $P = .001$), and this risk for patients in stage 3 at the beginning of chronic allograft dysfunction relative to stage 1 were 86.22 times ($P < .001$) (Figure 1b). Risk of death-censored graft loss with using cyclosporine plus mycophenolate mofetil was significantly lower than using cyclosporine plus azathioprine (RR=0.676, $P = .052$) (Figure 1c).

Discussion

In this retrospective single-center study, we examined the prognostic factors that affect long-term death-censored graft loss in patients with chronic allograft dysfunction.

Ponticelli and associates in a multivariate analysis showed donor age older than 45 years as a risk factor for late kidney allograft dysfunction (14). Lezaic and

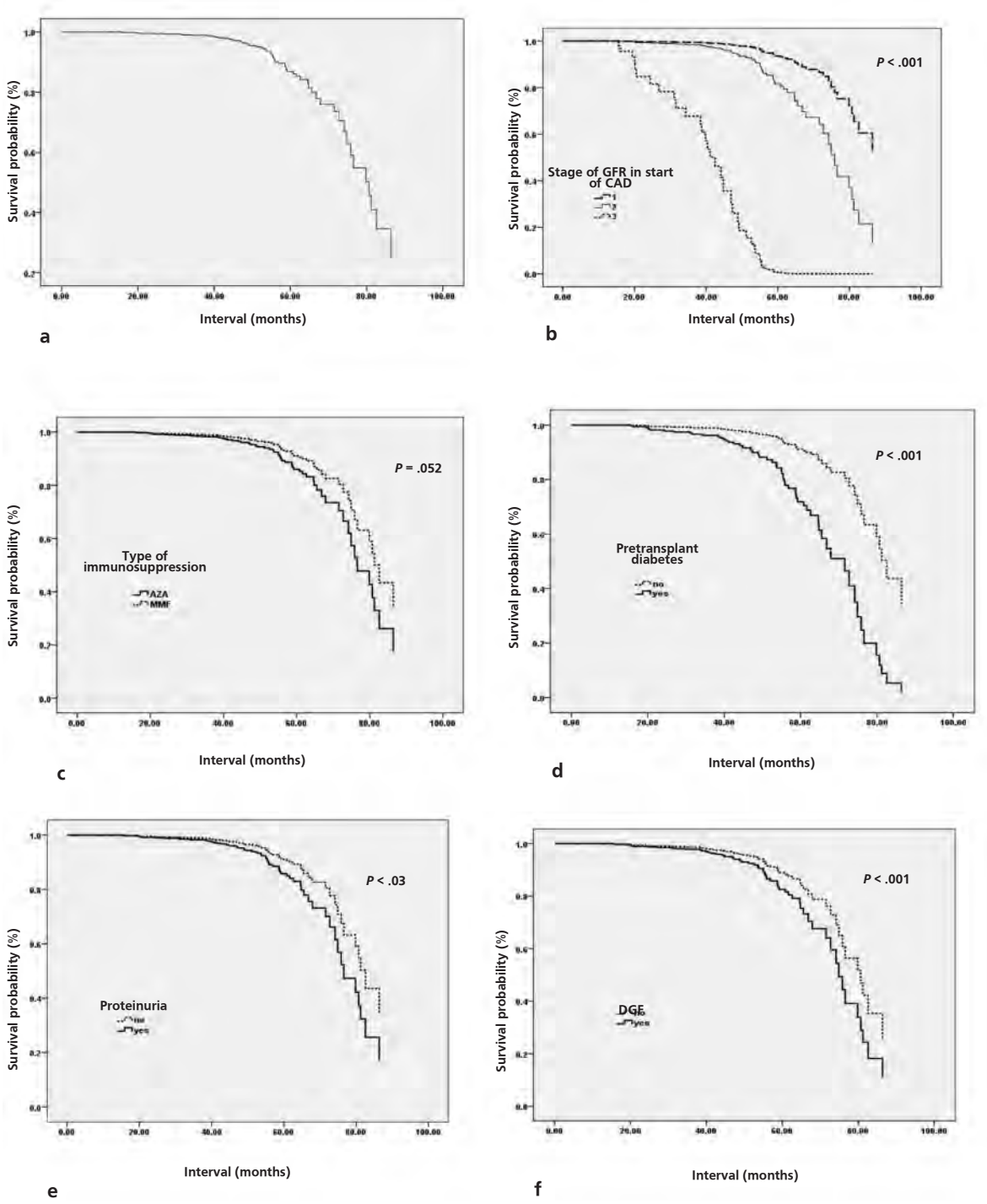

Figure 1. Death-censored graft loss, adjusted death-censored graft loss for significant risk factors in Cox regression. (a) The death-censored graft survival. (b) compare adjusted death-censored graft loss for 3 stage of glomerular filtration rate in start of chronic allograft dysfunction. (c) Compare adjusted death-censored graft loss for using CsA & MMF versus CsA & AZA. (d) Compare adjusted death-censored graft loss in pretransplant diabetes status. (e) Compare adjusted death-censored graft loss in proteinuria status. (f) Compare adjusted death-censored graft loss in DGF status.
Abbreviations: AZA, azathioprine; CsA, cyclosporine; DGF, delayed graft function; GFR, glomerular filtration rate; MMF, mycophenolate mofetil.

associates presented that worse graft outcome correlated positively with donor age, diabetes mellitus as underlying kidney disease, and initial immuno - suppression (15). Several papers have mentioned that donor age and history of diabetes significantly influence graft function (16-21). In agreement with other studies, we found that variables such as delayed graft function, proteinuria, kidney function in first year, and posttransplant hypertension significantly increase the risk of graft loss. Johnston and associates have

shown that short- and long-term graft survival have been significantly lower in delayed graft function and slow graft function group compared with the immediate graft function group (22).

Ponticelli and associates in univariate and multivariate analysis confirmed that delayed graft function, plasma creatinine at 1 year, pretransplant and posttransplant cardiovascular events, and pretransplant hypertension were significantly associated with late allograft failure (14). Scolari and associates in a retrospective analysis of 1169 deceased-donor kidney recipients have shown delayed graft function as a major risk factor for long-term graft survival (23). Other studies also confirm these findings (24, 25). In our study, the patients had a slow rate of decline in kidney function (chronic allograft dysfunction process). Patients who belonged to stage 2 and 3 at the beginning of chronic allograft dysfunction relative to patients who belonged to stage 1 had significantly more graft loss. The previous studies already pointed out that graft function at 6 or 12 months is a strong surrogate marker of long-term graft survival (14, 26, 27).

Scolari and associates showed that high creatinine levels at 6 months and 1 year after transplant, proteinuria, and cardiovascular risk factors are associated with poor allograft function (23). Gill and associates explored that patients with a higher baseline Cr had a small but significantly more rapid decline in glomerular filtration rate (28). Patients with proteinuria have increased risk of death-censored graft loss. Sancho and associates found that 5-year graft survival among patients with and without proteinuria were 69% and 93% (29). In a multivariate analysis, McLaren and associates showed that proteinuria at 1 year is a significant risk factor for late graft loss (30). Fernandez-Fresnedo and associates showed that graft survival in patients with proteinuria was significantly lower compared with patients without proteinuria (31). Kang and associates indicated that even a low level of proteinuria 1 year after transplant is an independent predictor of renal allograft loss (32). Several studies have implied that proteinuria is a marker of poor long-term allograft outcome (33-35). In our patients, proteinuria had a significant affect on late graft survival.

In previous studies, pretransplant diabetes and posttransplant hypertension conferred an increased risk for death-censored graft loss. Keane and associates suggested that glomerular hypertension and hyperfiltration are key factors in mediating progressive renal damage, because they have been shown to predict the development of microalbuminuria in diabetic and hypertensive kidneys (36). Gourishankar and associates examined using of mycophenolate mofetil versus azathioprine on the rate of change of CrCl beyond 6 months posttransplant. They found a more stable CrCl and a lower rate of loss of CrCl was associated with the use of mycophenolate mofetil versus azathioprine (27). Herwing-Ulf and associates showed that mycophenolate mofetil therapy conferred a decreased risk of late graft loss compared to azathioprine (29). We found less late graft loss in patients using mycophenolate mofetil versus azathioprine (37).

In summary, we found that age of donor, pretransplant hypertension, pretransplant diabetes, type of immunosuppression (mycophenolate mofetil vs azathioprine), delayed graft function, proteinuria, and stage of allograft dysfunction in start of chronic allograft dysfunction process are the major risk factors for late renal allograft dysfunction.

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