

# Factors Affecting Allograft and Patient Survival in Deceased Donor Kidney Transplantation: A Single Center Experience in Turkey

## *Kadavra Nakillerde Kısa ve Uzun Dönem Renal Sağkalıma Etki Eden Faktörler: Tek Merkez Deneyimi*

### ABSTRACT

**OBJECTIVE:** Renal transplantation is the treatment of choice in end-stage renal diseases. Long-term allograft function has remained steady in deceased donor kidney transplantation (DDKTx) during recent decades. In this study, we evaluated DDKTx outcomes at our hospital.

**MATERIAL and METHODS:** 72 cadaveric transplant patients who were grafted between January 2002 and October 2013 at our center were analysed retrospectively. Recipients and donors' demographic properties, immunologic and nonimmunologic characteristics, allograft function and emerging complications were examined. Factors associated with graft and patient loss were investigated.

**RESULTS:** Mean follow-up period was 60±38 months. Mean recipient age was 42±11 years, of which 51.4% was male. Dialysis vintage was 83±59 months, while mean cold ischemia time was 12±3 hours. One and five year graft and patient survival rates were 94.4%, 92.3% and 97.2%, 89.9% respectively. High serum creatinine value at discharge (p=0.003) and early surgical complications (p=0.041) were independent risk factors associated with poor graft survival. Having a recipient age ≥46 years (p=0.037) and cardiovascular disease (p=0.017) caused patient loss. Cardiovascular disease was independently associated with patient loss (HR=6.45[1.08-38.70], p=0.041).

**CONCLUSION:** In this study, it was demonstrated that creatinine value at discharge and early surgical complications were associated with allograft loss, while cardiovascular disease was associated with patient loss in DDKTx.

**KEY WORDS:** Deceased donors, Kidney transplantation, Allograft survival, Patient survival

### ÖZ

**AMAÇ:** Son dönem böbrek yetmezliğinde uygulanan renal replasman tedavileri içinde, en seçkin tercih böbrek naklidir. Çalışmada, merkezimizde yapılan kadavra böbrek nakli hastalarının sağkalım sonuçları araştırılmıştır.

**GEREÇ ve YÖNTEMLER:** Ankara Üniversitesi Tıp Fakültesi'nde Ocak 2002 ve Ekim 2013 tarihleri arasında yapılan ve izlenen 72 kadaverik böbrek nakli hastası retrospektif olarak taranmıştır. Alıcı ve vericilerin demografik verileri, immünolojik ve immünolojik olmayan özellikleri, allograft fonksiyonu ve geniş komplikasyonlar incelenmiştir. Graft ve hasta kaybı ile ilişkili faktörler değerlendirilmiştir.

**BULGULAR:** Ortalama takip süresi 60±38 aydır. Alıcıların ortalama yaşı 42±11 yıl, %51.4'ü erkektir. Nakil öncesi ortalama diyaliz süresi 83±59 aydır. Ortalama soğuk iskemi zamanı 12±3 saattir. Bir ve beş yıllık graft sağkalımı sırasıyla %94.4, %92.3; hasta sağkalımı %97.2, %89.9'dur. Hastaneden çıkış kreatinini yüksekliği (p=0.003) ve erken cerrahi komplikasyonların gelişimi (p=0.041) graft sağkalımını olumsuz etkileyen bağımsız risk faktörleridir. Alıcı yaşı ≥46 olması (p=0.037) ve kardiyovasküler hastalık gelişimi (p=0.017) hasta kaybını artırmaktadır. Kardiyovasküler hastalık gelişimi hasta kaybı için bağımsız risk faktörüdür (HR=6,45[1.08-38.70], p=0.041).

**SONUÇ:** Çalışmada, kadaverik böbrek nakillerinde hastaneden çıkış kreatinini yüksekliği ve erken cerrahi komplikasyonların gelişiminin allograft kaybını, kardiyovasküler hastalık gelişiminin hasta kaybını artırdığı gösterilmiştir.

**ANAHTAR SÖZCÜKLER:** Kadavra nakil, Böbrek nakli, Allograft sağkalımı, Hasta sağkalımı

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## INTRODUCTION

Kidney transplantation is the best treatment option for the patients with end stage renal disease (ESRD). In addition to cost-effectiveness (1), it provides a better patient survival (2) and quality of life in compare to dialysis. Although allograft and patient survival rates (SR) have been improved significantly in recent decades (3), in deceased donor kidney transplantation (DDKTx) allograft and patient SR are still less than that in living donor kidney transplantation (1,4). It has been determined that recipient and donor age (5), HLA mismatch (5), comorbidities (5), dialysis vintage (2), acute rejection (6) and adherence to immunosuppressants (7) are some factors identifying SR. In this study, it is aimed to analyze the DDKTx patients at our center and identify the factors affecting allograft and patient survival.

## PATIENTS and METHODS

A total of 91 DDKTx procedures were performed at the Renal Transplantation Unit of Ankara University School of Medicine from January 2002 to October 2013. Patients younger than 18 years and those with insufficient clinical data were excluded from the study, thus leaving 72 DDKTx patients to be evaluated.

Recipient characteristics (age at transplant, gender, body mass index [BMI], dialysis type and time before transplantation, primary renal disease), donor characteristics (age and gender), HLA-A, B, DR mismatches (MM), PRA positivity, cold ischemia time (CIT), posttransplantation immunosuppression treatment, hospitalization duration, early surgical and medical complications, delayed graft function and serum creatinine value at discharge were investigated. The HLA MM value ranges from 0 to 6 and was evaluated as 0 to 4 MM versus 5 to 6 MM. We also examined surgical complications including urinary obstruction, urine leak, urinary bleeding, lymphocele, vascular surgical problems including arterial thrombosis, renal vein thrombosis, and hemorrhage in the first posttransplantation month. Acute rejection episode, acute tubular necrosis, infection, blood transfusion, drug toxicity and leucopenia seen in the first posttransplantation month were also considered in the analysis.

All patients were followed at weekly intervals for the first 3 months, fortnightly for the next 3 months, monthly for the next 3 months, 3 monthly during the second year, and 6 monthly thereafter. Serum creatinine, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Formula, cytomegalovirus (CMV) and BK viremia, diabetes mellitus, hypertension, cardiovascular disease, other medical complications (hyperlipidemia, anemia, erythrocytosis, hyperuricemia, avascular necrosis, hyperparathyroidism, recurrent kidney disease, drug toxicity), infections, malignancies, acute rejection episodes and chronic allograft injury were included in the analysis at the 1st, 3rd, 6th, 12th months and yearly thereafter.

Patient survival is defined as the period from transplantation to death. Graft survival was defined as time period from

transplantation to requirement for dialysis or another transplantation. Recipient characteristics, donor characteristics, HLA MM, PRA positivity, hospitalization period, early surgical and medical complications, delayed graft function, serum creatinine value at discharge, cytomegalovirus (CMV) and BK viremia, new onset diabetes after transplantation, hypertension, cardiovascular disease, infections, malignancies, acute rejection episodes and chronic allograft injury were assessed in the analysis.

All the data obtained through this research were also shared using the Turkish Society of Nephrology Renal Transplantation Database.

## Immunosuppressive Regimen

All patients received induction therapy. Anti-thymocyte globulin (ATG) was used for the patients with high immunologic risk (n=11), while others received IL-2 receptor antagonists (n=61). The maintenance immunosuppressive protocol consisted of triple immunosuppression including corticosteroids, mycophenolate mofetil and tacrolimus.

All patients received prophylaxis against CMV infection (acyclovir or valgancyclovir), fungal infections (fluconazole or nystatin) and *Pneumocystis jirovecii* pneumonia (trimethoprim/sulfamethaxazole).

## Statistical Analysis

All statistical analysis was performed using SPSS software version 15 (SPSS Inc., Chicago, IL). Continuous variables were reported as mean and standard deviations (mean  $\pm$  SD), and percentages were used for categorical variables. Baseline characteristics among groups were compared using the chi-square test and Fisher exact test for categorical variables, and ANOVA for continuous variables. Survival analysis was conducted with Kaplan-Meier and Cox regression. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

The 72 recipients consisted of 35 (48.6%) females and 37 (51.4%) re males with a mean age of  $42.6 \pm 11.7$  years. The underlying disorders of ESRD were glomerulonephritis (n=22), diabetes mellitus (n=8), hypertension (n=7), and ESRD for unknown reason (n=30). Most of the patiens had received hemodialysis treatment (n=62) before DDKTx and only one had undergone a preemptive transplantation. Dialysis vintage was  $83.8 \pm 59.4$  months. The mean donor age was  $37.9 \pm 19.3$  years, 60% of whom were males. All transplantations at our center were ABO compatible. Twenty (27.8%) patients had HLA MM 5 to 6 MM and pretransplant PRA I or II positivity was seen in 12 (19.7%) patients. Mean CIT was  $12.2 \pm 3.0$  hours. After transplantation, patients stayed at the hospital for  $25.7 \pm 18.7$  days and the mean serum creatinine level at discharge was  $1.59 (0.5-12.7)$  mg/dL. Mean follow-up period was  $60.3 \pm 38.4$  months (Table I).

During the first month, we observed acute rejection (AR) episodes in 9 (12.5%) patients; if the whole follow-up period is taken into account, this reached 15 (21.8%) patients. 34 (47.2%) patients had delayed graft function (DGF), 38 (52.8%) had early medical complications and 15 (20.8%) had early surgical complications; including 2 urine leaks, 8 lymphoceles, 3 hematomas, and 2 arterial stenosis cases. Patients who experienced renal arterial thrombosis had early graft loss. Among the long-term complications, infections (66.7%), hypertension (58.3%), hyperlipidemia (56.9%) and anemia (52.8%) were seen for the most part (Table II).

Five patients (6.9%) had graft loss and patient loss was seen in 5 recipients (6.9%). One and five year graft SR were 94.4% and 92.3% respectively. The relevant variables associated with poor graft survival were high serum creatinine (Scr) value at discharge ( $p=0.001$ ) and early surgical complications ( $p=0.017$ ). In our multivariate analysis, both had an influence on graft survival ( $p=0.003$  ve  $p=0.041$ ) (Table III).

Patient SR at one year was 97.2% and at five years, 89.9%. Recipient age  $\geq 46$  years ( $p=0.037$ ) was a risk factor for patient loss. Among the complications seen at the whole follow-up, the only one associated with patient survival was the presence

**Table I:** Patient characteristics.

Variable		Deceased Donor Kidney Tx (n=72)
Age (years)		42.5 $\pm$ 11.7
Gender	Female (%)	35 (48.6)
	Male (%)	37 (51.4)
BMI (kg/m <sup>2</sup> )	<25	52 (73.2)
	25-29	19 (26.8)
	$\geq 30$	0 (0)
Primary renal disease	Unknown	22 (30.6)
	Hypertension	7 (9.7)
	Diabetes mellitus	8 (11.1)
	Glomerulonephritis	22 (30.6)
	Others	13 (18.0)
Renal replacement therapy (RRT)	Hemodialysis	62 (86.1)
	Peritoneal dialysis	7 (9.7)
	Preemptive	1 (1.4)
Dialysis vintage (months)		83.8 $\pm$ 59.4
Donor age (years)		37.9 $\pm$ 19.3
Donor gender	Female(%)	28 (40)
	Male(%)	42 (60)
HLA mismatches	0	4 (5.6)
	1	1 (1.4)
	2	10 (13.9)
	3	13 (18.1)
	4	24 (33.3)
	5	16 (22.2)
	6	4 (5.6)
PRA positivity	I	11 (15.3)
	II	6 (8.3)
	I or II	12 (19.7)
Cold ischemia time (hours)		12.2 $\pm$ 3.0
Hospitalization period (days)		25.7 $\pm$ 18.7
Serum creatinine at discharge (mg/dL)		1.59 (0.5-12.7)
First month MDRD-eGFR		62.3 $\pm$ 26.5
Follow-up period (months)		60.3 $\pm$ 38.4

**Table II:** Complications in kidney recipients.

Complications		Deceased Donor Kidney Tx (n=72)
<b>Early medical complications</b>	Infections (%)	24 (33.3)
	Acute rejection (%)	9 (12.5)
	Acute tubular necrosis (%)	7 (9.8)
	Transfusion (%)	10 (13.9)
	Total (%)	38 (52.8)
<b>Early surgical complications</b>	Urinary leak or lymphocele (%)	10 (13.9)
	Vascular (%)	5 (6.9)
	Total (%)	15 (20.8)
<b>Delayed graft function (%)</b>		34 (47.2)
<b>Acute rejection</b>	Antibody-mediated (%)	6 (8.3)
	Cell-mediated (%)	6 (8.3)
	Borderline (%)	3 (4.2)
	Total (%)	15 (21.8)
<b>Hypertension (%)</b>		42 (58.3)
<b>New-onset diabetes (%)</b>		13 (18.1)
<b>Hyperlipidemia (%)</b>		41 (56.9)
<b>Cardiovascular disease (%)</b>		14 (19.7)
<b>Anemia (%)</b>		38 (52.8)
<b>Erythrocytosis (%)</b>		5 (6.9)
<b>Hyperuricemia (%)</b>		13 (18.1)
<b>Avascular necrosis (%)</b>		6 (8.3)
<b>Hyperparathyroidism (%)</b>		16 (22.2)
<b>Recurrent kidney disease (%)</b>		1 (1.4)
<b>Drug toxicity (%)</b>		1 (1.4)
<b>Chronic allograft injury (%)</b>		4 (4.2)
<b>Infections (%)</b>		48 (66.7)
<b>Malignancy (%)</b>		4 (5.5)

of cardiovascular disease ( $p=0.017$ ). We have observed that presence of cardiovascular disease multiplies the risk of patient loss 6 times ( $HR=6.45[1.08-38.70]$ ,  $p=0.041$ ) (Table III).

## DISCUSSION

In our single center results of DDKTx, one and five year graft SR were 94.4% and 92.3%; patient SR was 97.2% and 89.9% respectively. Compared with European data; one- and five-year patient SR (97.4% and 91.8%) were similar, but graft SR (91.3%, 80.5%) was better in our DDKTx recipients (4). In

India, Kute et al. have found that one- and five-year patient and graft SR are 81.7%, 77.5% and 92.6%, 88.3%, respectively (8). In a study from Argentina, one and five year patient SR were 87.5% and 74.5%; graft SR were 91.6% and 64.7% respectively (9).

In their study, Fujita et al. have shown that graft survival is affected by donor age and early acute rejection (10). Diabetic nephropathy, donor and recipient age >45 years, dialysis time >7 years and HLA MM 4 to 6 were associated with lower graft

**Table III.** Multivariate analysis for graft and patient survival.

	Univariate p Value	Multivariate		
		HR	95% CI	p value
Graft survival				
Early surgical complications	0.017	15.11	1.12-203.60	0.041
Scr at discharge	0.001	2.40	1.36-4.25	0.003
Patient survival				
Recipient age ≥46 years	0.037	5.86	0.64-53.80	0.118
Cardiovascular disease	0.017	6.45	1.08-38.70	0.041

SR in Argentina (9). The risk factors for graft loss in DDKTx patients may differ by time; early losses were increased by AR, DGF and high PRA positivity, on the other hand late losses were correlated with advanced donor age and female donor gender (11). In our study, due to relatively low immunologic risk and limited number of patients, we have found no relation between graft survival and AR or immunologic factors. We have demonstrated the relationship with high Scr value at discharge and that early surgical complications are associated with allograft failure. It has been shown in previous studies that Scr value at discharge (2 mg/dL or less) has an inverse relationship with graft survival (11-14).

We have found no association between cold ischemia time (CIT) and graft survival. The UK Transplant Registry cohort has found that CIT is not associated with graft failure (15), which is consistent with USA Registry analyses (16). As CIT increased, an additional risk of graft loss has been identified for kidneys from circulatory-death donors than for those from brain-death donors (15). We haven't assessed the reason of donor death. Similar to our findings, data from the Collaborative Transplant Study have shown that CIT, when less than 18 hours, has no significant affect on graft survival (17).

Acute rejection is seen in 43.3-50.8% of DDKTx patients (18-21). The 10-year graft SR for patients who have a previous episode of AR is 45%, reduced significantly compared to the patients with no AR (19). AR has a significant adverse impact on deceased donor allograft survival (18-21), especially occurring after 3 months (20). Our patients have experienced less acute rejection episodes (21.8%), most likely because of their low immunologic risk. The improvement in short and long-term graft SR of DDKTx over the last decades is shown to be related to the decreased incidence of AR episodes (21). We have not detected a relationship between AR and graft SR, presumably due to the low incidence of AR and low number of patients.

The overall incidence of arterial thrombosis ranges between 0.4-3.0% and venous thrombosis between 0.4-3.4% in DDKTx patients (12-25). Deceased donor is a significant risk factor for developing renal allograft thrombosis along with donor age <6

or >60 years, recipient age <5-6 or >50 years, hemodynamic instability, peritoneal dialysis, recipient vessel atherosclerosis, diabetic nephropathy, a history of thrombosis, and DGF (24-26). Causing irreversible acute tubular necrosis, thrombotic complications are related with early graft failure (25,27). Early urinary complications such as ureteral necrosis and urinary leakage are seen at a rate of 4.6-8.7% in DDKTx patients (24,28-30). Although they are usually complicated with urinary tract infections (31), graft and patient SR are not affected by surgically-treated urinary complications (30,32,33). There are studies showing that graft SR is impaired in patients with surgical complications as in our study (34,35). Lempinen et al. have displayed that 5-year patient and graft SR are 88% and 74% in patients with surgical complications, and 92% and 87% in patients without surgical complications (34).

Arend et al. have displayed that mortality risk is higher for DDKTx patients aged over 40 years, male sex, smokers and in the presence of hypertension or diabetes (36). Poor patient survival is related with HLA MM 4 to 6, diabetic nephropathy, donor and recipient age >45 years and dialysis time >7 years in Argentina<sup>9</sup>. Although we have not observed a relationship between donor age, primary renal disease, HLA MM, comorbidities and SR, recipient age  $\geq 46$  years was similarly associated with poor patient survival in our study. We have found no effect of the type and duration of pretransplantation dialysis on post-transplantation mortality, in accordance with the results of a study of 916 DDKTx patients in the Netherlands (36).

Cardiovascular events have been shown to be the most frequent cause of death with function in DDKTx patients (37), especially after the first year of transplantation (36). During 2012 the mortality rate from cardiovascular disease was 3.5 per 1000 patient years in the United States, nearly twice that of infection or malignancy (1). In our study, like the Turkish Registry, the most common cause of death was infections (38). However, the presence of cardiovascular disease is the only independent risk factor for poor patient survival. It has been pointed out in the literature that recipient SR is shortened by cardiovascular disease (39).



In conclusion, it has been discovered in this study that a higher Scr value at discharge and early surgical complications are associated with allograft loss; and the presence of cardiovascular disease is associated with patient survival in DDKTx. Therefore, better screening and prevention strategies for cardiovascular disease might be a future goal for longer patient survival in DDKTx recipients.

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