Early Kidney Graft Loss: Etiology and Risk

Rūta Auglienė[1, 2], Dalinkevičienė Eglė[1, 2], Vytautas Kuzminskis[1, 2], Rima Maslauskienė[1, 2], Inga Arūnė Bumblytė[1, 2]

[1]Faculty of Medicine, Medical Academy of Lithuanian University of Health Sciences, Kaunas, Lithuania;
[2]Department of Nephrology, Lithuanian University of Health Sciences, Kaunas, Lithuania

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Abstract. *Background and objective: Successful kidney transplantation is optimal treatment for patients with end-stage renal disease (ESRD). However, early graft loss remains a devastating outcome for patients and health care specialists as a crucial cause of rapid return to dialysis and increased patient mortality. The aim of this study was to investigate the incidence, causes and associated risk factors for early graft loss in 90 days posttransplantation and to conduct a comparative analysis of cases when graft was lost early after transplantation with the ones functioning for more than 90 days.*

Methods: This retrospective study was performed at the Hospital of Lithuanian University of Health Sciences between May 2000 and December 2016. Of 375 adult transplantations from deceased kidney donors, 23 (6.1%) experienced early graft loss and 7 (1.9%) died with a functioning graft during 90 days after transplantation.

Results: Significant dissimilarity in the waiting time on dialysis before transplantation (54.78 vs. 31.39 months, P= 0.002), rate of delayed graft function (79.2% vs. 20.7%, P = 0.001), incidence of acute graft rejection (69.6% vs. 6.5%, P = 0.008), and infectious complications (82.6% vs. 45.7%, P = 0.003) were observed in early graft loss and graft survival > 90 days groups. Factors associated with early graft loss were identified: higher donor age (P = 0.040, r = 0.220), recipient duration of dialysis before kidney transplantation (P = 0.002, r = 0.371), delayed graft function (P = 0.001, r = 0.549), acute graft rejection (P = 0.007, r = 0.320) and infectious complications after transplantation (P = 0.003, r = 0.353). The multivariate analysis revealed recipient longer duration of dialysis before transplantation (P = 0.02, OR = 1.017) and a higher rate of infectious complications after transplantation (P = 0.011, OR = 4.386) as significant risk factors for early graft loss.

Conclusions: The incidence of early graft loss in our hospital has been decreasing in recent years. The most common cause of early graft loss in our center was transplant nephrectomy due to infectious complications, followed by acute graft rejection. Older donor age, expanded criteria donor type, waiting time for deceased donor kidney transplantation, delayed graft function, posttransplant infections, and acute rejection are associated with early graft loss.

Introduction

Successful kidney transplantation is optimal treatment for patients with end-stage renal disease (ESRD) due to the improved quality of life, longer patient survival and reduced health care costs as compared with sustained dialysis [1, 2]. There has been an evident improvement in renal transplantation outcomes over the last decades associated with advanced surgical approaches and medical care, improved immunosuppressive regimens, prophylaxis and management of infections, and other complications [3, 4].

Early graft loss (EGL) remains a devastating outcome for patients and health care specialists as a crucial cause of rapid return to dialysis and increased patient mortality. It is caused by a range of etiologies and occurs in approximately 9% of transplants [3, 5] during the first year after transplantation. Causes include patient vascular events, acute graft rejection, primary non-function, life-threatening infections, and death with a functioning graft. The incidence of renal transplant thrombosis ranges between 0.1% and 8.4% in the first year after transplantation and accounts for at least one-third of all graft failures within 3 months [6]. Acute graft rejection rates after kidney transplantation have declined over the last years [7]; therefore, recently more attention is brought to the high incidence of death with a functioning graft. Death with a functioning kidney transplant occurs in 2–5% of patients each year [7] and is almost as frequent as graft failure in the first-year posttransplant [8]. The leading reason for death with a functioning graft is cardiovascular events, followed by different infectious complications [8, 9].

The aim of this study was to investigate the incidence, causes and associated risk factors for early

Corresponding author: Rūta Auglienė, Department of Nephrology, Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Eivenių 2, 50009, Kaunas, Lithuania
E-mail: ruta.augliene@lsmuni.lt

graft loss in 90 days posttransplantation and to conduct a comparative analysis of cases when graft was lost early after transplantation with the ones functioning for more than 90 days. Another objective was to examine the incidence of death with a functioning graft for the first time at a major Lithuanian transplantation center during 16 years of observation.

Materials and Methods

This retrospective, observational cohort study included all adult deceased donor kidney transplant procedures performed at the Hospital of Lithuanian University of Health Sciences between May 2000 and December 2016. During this period, 380 deceased donor kidney transplantations were performed. One dual kidney transplant (using the *en-bloc* technique) and 4 transplantations with incomplete clinical data were excluded, leaving a final cohort of 375 recipients and 207 their kidney donors for further analysis.

Information concerning donor's age, gender, donor cause of death, history of hypertension, serum creatinine level before procurement, cold ischemia time, and donor type (expanded criteria or standard) were included in the analysis. Recipient's data involved age, gender, duration of dialysis before transplantation, HLA mismatch, body mass index, history of diabetes, acute rejection, and posttransplantation infectious complications. Presence of delayed graft function (DGF) [10] was defined as a need for dialysis first week after transplantation.

Early graft loss (EGL) was defined as loss of kidney transplant function resulting in returning to dialysis within 90 days after transplantation. Cases when kidney transplant function was lost due to recipient death within 90 days after transplantation were not included in the EGL group. The non-EGL group was randomly selected from the cases with a functioning renal transplant during 90 days after transplantation. A comparative analysis of the EGL group versus the non-EGL group was performed to reveal the differences in donor and recipient characteristics in both groups.

EGL was diagnosed according to the criteria listed below. The diagnosis of arterial or venous thrombosis was suspected by Duplex ultrasound examination and confirmed during explantation or by histological graft analysis after transplant nephrectomy. Early graft loss due to acute rejection was confirmed by transplant biopsy and defined as irreversible worsening of graft function requiring dialysis without response to immunosuppressive treatment. Primary non-function was defined as lack of transplant function from the time of transplantation in the well-perfused kidney (confirmed by Duplex ultrasound examination) without other biopsy proven causes of non-function and necessitating dialysis after kidney transplantation.

Death with a functioning graft was defined as recipient death 90 days post-transplantation with a functioning kidney transplant.

Statistical data analysis was performed using SPSS software. The groups were compared using the independent samples *t* test and the chi-square test. Univariate and multivariate analyses were conducted using nonparametric Spearman correlation and binary logistic regression methods. A two-sided *P* value of 0.05 was statistically significant.

Results

Donor and Recipient Characteristics

The majority of the deceased kidney donors were men (60.1%) with cerebrovascular disease (55.8%) as the main cause of death. The mean donor age was 43.28 ± 16.00 years (range, 6 to 75), 12.8% of donors were older than 60 years. Expanded criteria donor kidneys were transplanted in 30.8% of the cases. The mean cold ischemia time was 18.49 ± 4.99 hours (range, 6.5 to 32).

Table 1. Donor demographics

Donor variable	Period of kidney transplantation				
	2000–2004	2005–2007	2008–2010	2011–2013	2014–2016
	n = 26	n = 43	n = 34	n = 49	n = 55
	Mean ± SD (median) or %				
Age, years	40.84 ± 13.69	37.09 ± 15.11	44.88 ± 15.91	46.45 ± 14.79	44.26 ± 17.43
Gender (male/female), %	57.7/42.3	72.1/27.9	52.9/47.1	61.2/38.8	56.6/43.4
Cause of death (cerebrovascular disease/trauma), %	50.0/50.0	47.6/52.4	63.3/36.7	69.4/30.6	59.6/30.4
History of hypertension (yes/no), %	23.1/76.9	16.7/83.3	48.3/51.7	32.6/67.4	32.7/67.3
Expanded criteria donor (yes/no), %	19.2/80.8	23.8/76.2	39.4/60.6	39.6/60.4	35.9/64.2
Terminal serum creatinine, μ*mol/L*	101.32 ± 49.64 (91.00)	106.62 ± 41.96 (98.00)	94.69 ± 52.01 (83.00)	102.04 ± 46.43 (87.00)	93.33 ± 47.81 (81.00)

*Donor age was normally distributed.
Terminal serum creatinine was not distributed normally in all periods of kidney transplantation.

Table 2. Recipient demographics

Recipient variable	Mean ± SD (median) or %
Age, years	45.41 ± 11.71
Gender (male/female), %	56.9/43.1
Body mass index, kg/m^2	25.19 ± 4.60
Duration of dialysis, months	35.11 ± 28.71 (25.00)
History of diabetes (yes/no), %	14.2/85.8
HLA mismatch (< 3/⩾ 3), %	60.4/39.6
Cold ischemia time, hours	18.49 ± 4.99 (19.00)
Delayed graft function (yes/no), %	28.2/71.8
Graft rejection (yes/no), %	10.3/89.7
Infectious complications (yes/no), %	48.4/51.6

*Recipient age and body mass index were normally distributed. Duration of dialysis and cold ischemia time were not distributed normally.

The average recipient age was 45.41 ± 11.71 years (range, 18 to 77) with 56.9% of men. Delayed graft function was observed in 28.2% of cases. Donor and recipient demographics are presented in Table 1, 2.

Incidence and Causes of Early Graft Loss

During the 16-year study period, EGL during 90 days after transplantation occurred in 23 recipients (6.1%). Causes of EGL following kidney transplant nephrectomy included infectious complications (9; 2.4%), acute rejection (6; 1.6%), arterial and/or venous thrombosis (3; 0.8%), hemorrhage (3; 0.8%), primary non-function (1; 0.3%), and cortical necrosis (1; 0.3%). Infectious complications involved sepsis caused by fungal infection, kidney transplant abscess, and acute pyelonephritis due to immunodeficiency and peritonitis.

Comparative Snalysis of EGL and Non-EGL Groups

The study population was divided into 2 groups according to the presence of early graft loss. The analysis was performed in the EGL group (n = 23, graft survival less than 90 days) and in the randomly selected group without observed early graft loss (the non-EGL group) (n = 64, graft survival more than 90 days). Patients who developed early graft loss had a longer duration of dialysis before transplantation (54.78 vs. 31.39 months, $P = 0.002$) and a higher rate of delayed graft function after transplantation (79.2% vs. 20.7%, $P = 0.001$) as compared with kidney transplants lasting more than 90 days. The incidence of acute graft rejection episodes (69.6% vs. 6.5%, $P = 0.008$) and infectious complications (82.6% vs. 45.7%, $P = 0.003$) were also higher in the early graft loss group. No other significant differences in donor and recipient factors within the EGL group and the non-EGL group were found (see Table 3).

Table 3. Donor and recipient characteristics in EGL and non-EGL groups

Variable	Graft survival		*P* value
	EGL group (< 90 days) Mean ± SD or %	Non-EGL group (> 90 days) Mean ± SD or %	
Donor			
Age, years	47.17 ± 10.85	39.42 ± 16.85	0.140
Gender (male/female), %	45.8/54.2	64.1/35.9	0.121
Cause of death (cerebrovascular disease/trauma), %	31.2/68.8	43.6/56.4	0.132
History of hypertension (yes/no), %	37.5/62.5	26.7/73.3	0.327
Expanded criteria donor (yes/no), %	20.8/79.2	18.8/81.2	0.826
Terminal serum creatinine, umol/L	93.33 ± 21.91	92.62 ± 41.60	0.919
Cold ischemia time, hours	18.55 ± 5.19	18.50 ± 4.99	0.976
Recipient			
Age, years	47.50 ± 9.39	47.27 ± 13.18	0.937
Gender (male/female), %	54.2/45.8	62.5/37.5	0.477
Body mass index, kg/m^2	26.80 ± 3.89	25.34 ± 4.65	0.176
Duration of dialysis, months	54.78 ± 33.87	31.39 ± 24.71	0.002
History of diabetes (yes/no), %	8.7/91.3	13.0/87.0	0.595
HLA mismatch (<3/⩾3), %	82.6/17.4	88.9/11.1	0.470
Delayed graft function (yes/no), %	79.2/20.8	20.7/79.3	0.001
Acute graft rejection (yes/no), %	69.6/30.4	6.5/93.5	0.008
Infectious complications (yes/no), %	82.6/17.4	45.7/54.3	0.003

Table 4. Univariate analysis of risk factors of early graft loss

Variable	*Spearman* correlation coefficient r	*P* value
Donor		
Age (per year)	0.220	0.040
Female gender	0.165	0.124
Traumatic cause of death	0.051	0.727
History of hypertension	0.107	0.332
Expanded criteria donor	0.024	0.828
Terminal serum creatinine	0.009	0.937
Cold ischemia time	0.003	0.976
Recipient		
Age (per year)	0.009	0.937
Female gender	0.076	0.483
Body mass index	0.147	0.176
Duration of dialysis (per month)	0.371	0.002
History of diabetes	–0.064	0.601
HLA mismatch ⩾ 3	0.088	0.477
Delayed graft function	0.549	0.001
Acute graft rejection	0.320	0.007
Infectious complications	0.353	0.003

Associated Risk Factors for Early Graft Loss

The univariate analysis revealed that higher donor age ($P = 0.040$, r = 0.220), recipient longer duration of dialysis before kidney transplantation ($P = 0.002$, r = 0.371), delayed graft function after transplantation ($P = 0.001$, r = 0.549), acute graft rejection ($P = 0.007$, r = 0.320) and infectious complications after transplantation ($P = 0.003$, r = 0.353) were significantly associated with EGL (see Table 4).

In the multivariate logistic regression analysis, recipient longer duration of dialysis before transplantation ($P = 0.02$, OR = 1.017) and a higher rate of infectious complications after transplantation ($P = 0.011$, OR = 4.386) were significant risk factors for EGL (see Table 5).

Etiology of Death With a Functioning Graft

During the observation period in the year 2000–2016, 34 patients (9%) died with a functioning kidney transplant. In the period of 90 days posttransplantation, 7 patients (1.9%) died with a functioning graft. The causes of death with a functioning graft were cardiovascular (4; 1.1%), infectious (2; 0.53%), and cerebrovascular (1; 0.27%).

Most patients who died from myocardial infarction were men (3; 0.8%), 45–66 years old, and one of them had previous cardiovascular events (angina pectoris). The only female patient, aged 45, had a history of diabetes type 1. The duration of dialysis before transplantation varied from 12 to 36 months in the myocardial infarction group. Infectious complications that caused patient's death included septic shock due to fulminant pneumonia (10 days after transplantation) and bacterial complications after influenza infection (20 days after transplantation). Both patients had only 2 HLA mismatches and both received the same immunosuppressive therapy (basiliximab with mycophenolate mofetil and steroids as an induction immunosuppressive therapy, maintenance immunosuppression consisted of cyclosporine plus mycophenolate mofetil and steroids). The duration of dialysis before transplantation lasted for 39 months and 94 months in the infectious complications group. Ischemic stroke caused death with a functioning graft for one 35-year-old female diabetic patient, who was on dialysis for 15 months before transplantation.

Discussion

We acknowledge the weaknesses of this retrospective, single-center study. However, the one center study decreases the confounding effects of multiple transplantation and surgical protocols. During the 16 years of the study period, important changes in the immunological approach, immunosuppressive therapy, and surgical techniques have been made, which can lead to issues when comparing transplantation data from different time intervals.

The aim of this study was to investigate the incidence, causes and associated risk factors for early graft loss in 90 days posttransplantation and to conduct a comparative analysis of cases when graft was lost early after transplantation with the ones functioning for more than 90 days.

The most common cause of early graft loss in our center was transplant nephrectomy due to infectious complications (mainly life-threatening bacteremia). Urinary tract infections (UTIs) can lead

Table 5. Multivariate logistic regression analysis of risk factors of early graft loss

Variable		Odds ratio	95% CI	*P* value
Duration of dialysis (per month)		1.019	1.006–1.032	0.005
Infectious complications	no	1	–	–
	yes	4.725	1.540–14.500	0.007
Constant -4.215				

to pyelonephritis and bacteremia and are associated with early graft loss and decreased patient survival [11]. According to previously published data, the incidence of UTIs in the first year after transplantation varies in the range 22.7–34% [12, 11], and bacteremia during 3 months posttransplantation can be observed in more than a half of cases [11]. When performing kidney transplantation, ureteral stents in ureter-bladder anastomosis are used to avoid urinary leak and ureteral stricture. However, the microbial colonization of ureteral stents in the immunosuppressive state increases the risk of urinary tract infections, bacteremia, and early graft dysfunction [13]. It is clear that kidney transplant patients are more susceptible to various infections than the general population, and immunosuppressive treatment in an early posttransplantation period plays an important role.

On the other hand, the use of intense immunosuppressive regime with the initiation of mycophenolic acid and tacrolimus followed by more sensitive HLA-matching techniques is related to a decreasing rate of acute rejection. Both cellular and antibody-mediated acute kidney transplant rejections adversely affect graft survival in the first year after transplantation [14, 4] and remain an independent risk factor for early graft loss and decreased transplant survival [15]. According to previously published data, acute graft rejection rates during the early posttransplantation period are in the range of 9.9–30% [14, 16] and depend on immunosuppressive strategy. In our study, the incidence of early graft loss caused by acute graft rejection is rather low (9.1%) and it occurred only during the first years of the start of the kidney transplantation program [17]. This can explain our higher incidence of early graft loss caused by infections due to potent immunosuppressive treatment.

Another group of factors causing early graft loss involves vascular thrombosis and hemorrhagic complications. The incidence of vascular thrombosis and hemorrhage that resulted in transplant nephrectomy in our center is matching with other reports [6,18]. Vascular and hemorrhagic complications can be associated with technical problems during surgical implantation, as well as donor and recipient factors. Unfortunately, due to the lack of detailed data concerning transplantation operation, surgical factors could not be evaluated in our study.

Primary graft non-function leading to early graft loss was observed in rather low rates in our study, but it can be explained by improved diagnostic options to determine the cause of transplant loss.

Our data revealed that patients in the EGL group, compared with those in the non-EGL group, were waitlisted for a kidney transplant for a longer time, had a higher incidence of delayed graft function (DGF), acute rejection and infection episodes during 90 days after transplantation.

We performed analysis to reveal the association of donor and recipient factors with early graft loss 90 days after transplantation. Increasing donor age, longer recipient waiting time on dialysis, delayed graft function, acute graft rejection and infection episodes are related to early graft loss during 90 days posttransplantation. Infection episodes and each month of waiting time on dialysis predict early graft loss in 90 days posttransplantation. Previous studies analyzed support these facts of the negative impact of older donor age, acute rejection and infection episodes on early graft loss and first-year kidney transplant survival [17, 19]. Other authors agree that DGF is associated with a poorer kidney transplant function and decreased graft survival in the first year posttransplantation [20, 10]. Moreover, an association between DGF and acute graft rejection with transplant failure has been published, but we could not support these findings for early graft loss in our study [15]. Another important factor – longer waiting time on dialysis for a kidney transplant – is also responsible for shorter graft survival and all-cause patient mortality [22]. What is more, waiting time for a deceased donor kidney transplant continues to rise and the shortage of optimal donors necessitates the use of kidneys from expanded criteria donors. Kidneys from expanded criteria donors are associated with early graft loss and poorer short- and long-term outcomes [17, 21, 18].

Another objective was to examine the incidence of death with a functioning graft for the first time at a major Lithuanian transplantation center during 16 years of observation. The past history of cardiovascular events and diabetes are significant risk factors for cardiovascular death with a functioning graft in the early period posttransplantation [22–24]. Our study revealed that the incidence of death with a functioning graft in the early period after transplantation was in line with the experience of other transplantation centers [25, 26].

Conclusions

Although early graft loss is an undesirable event associated with decreased kidney transplant and patient survival, it has become less common in our hospital in recent years. The most common cause of early graft loss in our center was transplant nephrectomy due to infectious complications, followed by acute graft rejection. Older donor age, expanded criteria donor type, waiting time for deceased donor kidney transplantation, delayed graft function, post-transplant infections, and acute rejection are associated with early graft loss.

Ethics statements

This study was approved by the local ethical committee (Lithuanian Bioethics Committee BE 2-9).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Authors' contributions

AR: conception and design, data collection and analysis, manuscript writing and final approval of the manuscript; DE: conception and design, data collection and analysis; KV: conception and design, critical revision and final approval of the manuscript; MR: data collection, drafting of the manuscript; BIA: conception and design, critical revision and final approval of the manuscript. All authors made significant intellectual contributions and approved the final manuscript.

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