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Original Article

Early graft survival after renal transplantation, single center experience

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ABSTRACT

Aim: The best treatment for patient with end stage kidney disease is kidney transplantation which improve their quality of life and survival rate. The aim of our study is to determine the factors that affect the results of early outcomes of graft function.

Method: Twenty-eight adult patients who underwent renal transplantation from 2016 to 2017 were included in our university.

Results: The median age of the recipients was 38.5 (range: 19-65) and 68% (19 patients) were male. Acute rejection was detected in 8 patients. Patients who developed rejection were found to have higher panel reactive antibody positivity and higher parathyroid hormone levels. Panel reactive antibody positivity was found to be 25% in patients who developed rejection and 0% in patients who did not develop rejection *($p = 0.02$)*. The parathyroid hormone level was calculated as 963.2 ± 587 in the rejection group and 378 ± 227 in the rejection group *($p = 0.003$)*. It was observed that 37.5% of DM patients had rejection and 10% in non-diabetic patients. The difference was statistically significant *($p = 0.08$)*.

Conclusion: Panel reactive antibody positivity and parathyroid hormone levels increased the likelihood of rejection. The effect of the presence of diabetes mellitus in the patient on the development of rejection was observed to be limited. Our findings were consistent with the literature. Because of the number of patients and the short follow-up period, further studies are needed.

Keywords: Renal transplantation, acute rejection, graft survival, graft failure.

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Introduction

Renal transplantation has been preferred for better survival and quality of life in patients with end-stage renal diseases [1]. Studies have shown that many donor and recipient factors affect patient survival after transplantation. Some of these factors include age, gender, body weight, number of human leukocyte antigen (HLA) mismatches, duration of warm ischemia, development of acute rejection, delayed graft function, general health status, proteinuria, albumin level, Panel Reactive Antibody (PRA), new onset hypertension (HT), diabetes mellitus (DM), hyperlipidemia, cytomegalovirus, hepatitis B, hepatitis C infections, serum uric acid level, gene polymorphisms (Caveolin 1,

chemokine receptor 5 polymorphism, etc.) and serum homocysteine levels [2-10].

Studies on early graft survival after renal transplantation are important in terms of contributing to long-term outcomes. Pre-transplant blood product transfusion history may result in HLA antigen sensitization. The highest risk for sensitization occurred in multipara women, multiple transfusions and failed organ transplants. Frequent transfusion also caused an increase in PRA. The pro-inflammatory condition adversely affects graft survival [11,12].

In the preoperative era, imaging of renal vascular system is important for surgical success and graft survival. Transplantation using multiple renal artery grafts is as safe as single-artery grafts when evaluated for urologic complications [13]. Another factor related to the survival of the transplanted kidney is the age of the recipient and donor. Renal recipients over 60 years of age have an increased risk of graft failure [14]. Graft failure and long-term mortality have also increased in recipients of older donors compared to younger kidney donation cases [15]. The incidence of early graft failure in obese recipients is probably increased because of vascular suture problems [16,17]. Previous or active smoking is associated with decreased patient and graft survival and increased rejection rate [18]. Although diabetes is a common cause of end-stage renal disease, new-onset diabetes mellitus after transplantation can be an important complication of renal transplantation via affecting the survival of allograft by increasing cardiovascular risk [19-22]. Low post-dialysis systolic blood pressure and low pre-dialysis diastolic blood pressure were associated with decreased risk of death, whereas post-dialysis high diastolic blood pressure was associated with increased risk of death. Low blood pressure before transplantation was also associated with decreased risk of graft failure [23]. Ischemia reperfusion injury after renal transplantation affects short-term and long-term graft outcomes. Ischemia reperfusion injury is associated with delayed graft function, graft rejection, chronic rejection and chronic graft dysfunction [24].

Studies based on protocol biopsies have shown that acute rejection of both cellular and humoral type may lead to long-term changes due to reduced graft survival [25-28]. Compared with patients without acute rejection, those with acute rejection in the first year were observed more frequently in patients with HLA mismatches [29]. Decreased early graft function after kidney donation from live donors was found to reduce graft survival without rejection. However, the effect on graft survival in the long term is uncertain [30]. Therefore, we conducted a retrospective study to show the factors affecting early graft survival after renal transplantation in our institution.

Materials and Methods

The study was enrolled 28 sequential adult cases who underwent kidney transplantation from the living donor between 2016 and 2017 at transplantation clinic of our University Hospital. We also enrolled data of 28 donors. The study was designed retrospectively. The study was conducted in accordance with the ethical approval of the University Ethics Committee (Decision number: 29032017-4). The data were obtained from the hospital database and patients' files. Age, gender, additional diseases, weight, height and laboratory test results were recorded.

For the statistical analyzes, IBM SPSS (Statistical Package for the Social Sciences) Version 16.0 software was used. In the study, numerical data are given as median (range).

Categorical and non-parametric variables were analyzed with Chi-square test and Mann Whitney U test, respectively. Statistical first type error margin (α) was taken as 0.05 for this study. Therefore, the results for p <α were considered statistically significant at 95% confidence level.

Results

The median age of the recipients was 38.5 (range: 19-65) years and 68% of the subjects (19 patients) were male. Fifty percent (14 patients) had a history of cigarette smoking. The median body mass index of the patients was 23 (range: 16-34) kg/m^2. Hypertension and diabetes mellitus were in 46% and 18% of the patients. Glomerulonephritis was the etiologic factor of end stage renal disease in the remaining subjects. When ABO blood groups were examined, it was observed that 54% have A, 21% have B, and 25% have 0 group type. Besides, 89% of the patients were Rh + and remaining were Rh-.

Median creatinine and GFR values of graft kidneys at 0, 3 and 6 months were given in Table 1.

Table 1. The creatinine and GFR values of the grafts at 0, 3 and 6 months after transplantation.

Parameters	0 months	3 months	6 months
Creatinine (mg / dl)	1.26	1.29	1.19
GFR (ml / min / 1.73 m2)	65	64	70

The median age of the donors was 48.5 (Range: 25-72) years and 57% were women. 57% of the donors had a history of smoking. The median body mass index of the donors was calculated as 26 (Range: 18-33) kg/m^2. When ABO blood groups were examined, it was observed that 43% were A, 11% were B and 46% were 0. There was no donor from the AB blood group. Also, 86% of the donors were Rh +. Two donors (7%) had polar arteries. In terms of compliance of donors and patients, 11 (39%) patients were the same gender with donor, 22 (79%) were have the same ABO blood group, and 23 (82%) were have similar Rh type with donor. Twenty-two (79%) of the donors were relatives, and there was no relation between the 6 of the donors.

Table 2. Recipient factors that may affect rejection.

Parameters	Rejected	Unrejected	*P*
Recipient age Year ± standard deviation	35,8±16	41,9±12,4	*0,30*
Gender of the recipient • male • female	5 (63) 3 (37)	14 (70) 6 (30)	*0.70*
Smoking • smoked • non-smoked	4 (50) 4 (50)	10 (50) 10 (50)	*1*
DM history • yes • no	3(37,5) 5(62,5)	2(10) 18(90)	*0,08**
HT history • yes • no	5(62,5) 3(37,5)	8(40) 12(60)	*0,41*
Pregnancy history • yes • no	2 2	2 4	*0,34*
History of blood transfusion • yes • no	2(28,6) 5(71,4)	6(30) 14(70)	*0,94*
Previous transplantation history • yes • no	1(12,5) 7(87,5)	1(5) 19(95)	*0,48*
Presence of Class II Panel Reactive Antibody • positive • negative	2(25) 6(75)	0 20(100)	*0,02**
Induction therapy • given • none	2(25) 6(75)	8(40) 12(60)	*0,45*
Patient body mass index (kg / m2)	21,9±5,3	24,4±4,8	*0,15*
Parathormone level (mg/dl)	963,2±587	378±227	*0,003**
Dialysis time median (range), (weeks)	0 (0-104)	1,5 (0-78)	*0.50*

A total of 8 (28.5%) acute rejections were seen. When the patients with and without rejection were compared, there was no difference in urine output before transplantation, duration of dialysis before transplantation, patient age, gender, body mass index, smoking history, ejection fraction, history of hypertension, blood transfusion and previous renal transplantation (Table 2).

The presence of panel reactive antibodies and parathyroid hormone levels were different in patients with acute graft rejection. Both of the 2 patients with positive panel reactive antibody had rejection, but only 6 of the 26 patients with negative PRA had rejection *(p= 0.02)* (Table 2). In addition, patients with acute rejection had higher parathyroid hormone levels than patients without rejection. The mean parathyroid hormone level was 963.2 ± 587 in the rejection group and 378 ± 227 in the rejection group *(p = 0.003)* (Table 2).

It was observed that patients with a history of DM developed rejection with a frequency of 37.5% and this rate was observed as 10% in patients without a history of DM. The difference was close to statistical significance, yet, insignificant *(p =0.08)* (Table 3).

When the patients with and without rejection were examined, it was found that the age, sex, smoking status, CMV status, warm ischemia time, donor glomerular filtration rate, donor body mass index and presence of polar artery did not affect the development of rejection (Table 3). Similarly, it was found that gender accordance between donor and recipient, having the same ABO blood type, having the same Rh blood type, and the number of incompatible HLA mismatch did not affect the presence of rejection (Table 3). When the effect of the relationship between the donor and the recipient on the rejection was investigated, it was seen that in all patients having rejection,

Table 3. The factors related to donor and recipient/ donor compatibility that may affect rejection.

Parameters	Rejected	Unrejected	*P*
Donor age	42.8±10,6	49.3±11.7	*0.14*
Donor gender • **male** • **female**	3(37,5) 5(62,5)	9(45) 11(55)	*0,70*
Donor body mass index (kg / m2)	24,9±4,9	26,5±3,5	*0,37*
Donor smoking • **smoked** • **non smoked**	4 (50) 4 (50)	12 (60) 8 (40)	*0,63*
Number of HLA mismatches	2,9±1,3	3±1,5	*0,91*
Donor glomerular filtration rate (ml / min / 1.73 m2)	111,7±21,4	103±13,5	*0,18*
Polar artery • **yes** • **no**	1(12,5) 7(87,5)	1(5) 19(95)	*0,48*
Donor CMV IgG • **positive** • **negative**	8(100) 0	19(95) 15	*0,52*
Warm ischemia time, min	14,4±0,8	14.5±1.1	*0,83*
Relation • **relative** • **unrelated**	8(100) 0	14(70) 6(30)	*0,08**
Gender match • **incompatible** • **compatible**	4(50) 4(50)	7(35) 13(65)	*0,46*
ABO match • **incompatible** • **compatible**	1(12,5) 7(87,5)	5(25) 15(75)	*0,46*
Rh match • **incompatible** • **compatible**	1(12,5) 7(87,5)	4(20) 16(80)	*0,64*

the transplantation was from the relative donor. No rejection was observed in any of the 6 patients who received transplantation from non-relative donors. The results were close to statistical significance, yet, insignificant *(p = 0.08)* (Table 3).

Discussion

Renal transplantation has recently been preferred for better survival and quality of life in patients with end-stage renal disease [1]. Studies on early graft survival after renal transplantation are important in terms of

contributing to long-term outcomes. In a study with a follow-up of 122 months after renal transplantation, a correlation was found between proteinuria (calculated with protein creatinine ratio) and poor graft function in the first 3 months. The advantage of this study is long follow-up period and especially values higher than 0.5% of protein creatinine ratio have been found to be observed more frequently in vascular events [31]. No correlation was found in our study between rejection and micro-albumin/creatinine ratio in spot urine at 0, 3 and 6 months. The lack of correlation with respect to graft survival may be due to our lower follow-up.

One of the issues that can be important in the anamnesis is the history of blood product transfusion before transplantation. Erythrocyte transfusion may result in HLA antigen sensitization. The highest risk for sensitization occurred in multipara women, multiple transfusions, and failed organ transplants, but previous data have shown equal or greater risk for men. As a result, an increase in PRA is associated with poor graft survival [11, 12]. In our study, no correlation was found between the recipient's blood product transfusion history and the number of incompatible HLAs between the recipient and the donor, while rejection developed in 2 of the 2 patients with panel reactive antibody positivity. The ratio of PRA positivity was 25% among patients who developed rejection and 0% in patients who did not develop rejection. Our findings are compatible with the literature.

Another factor related to the survival of the transplanted kidney is the age of the recipient and donor. Renal recipients have an increased risk of graft failure, especially with age greater than 60 years [14]. When kidney donors are examined, it is seen that graft failure and long-term mortality are increased in the recipients of older donors compared to younger donor cases. However, these recipients appear to be better or more accomplished than those of the kidneys of donors with standard or extended criteria [15]. When we examined our patients with and without rejection, it was found that the age of the donor did not affect the development of rejection. This may be due to younger age of our patients and donors.

Early results up to one year after kidney transplantation may also be affected by the nutritional status of the recipients. In our study, we found significantly higher rates of early graft failure in both thinner and overweighed recipients. The incidence of early graft loss increases in those recipients and may be due to the more frequent technical problems of the operation in obese patients [16, 17]. In our study, we could not show any relationship between increase in body mass index and rejection rate probably due to no obese patients was present in our cohort.

When we examine the effects of smoking on endothelial damage and its effect on delaying or even preventing the healing process; previously or active smoking is associated with decreased patient and graft survival and increased rejection rate [18]. It was shown that the smoking of the donor and the recipient was not significant between the patients with and without rejection. This may be due to the short follow-up period.

Although diabetes is a common cause of end-stage renal disease, new-onset diabetes after transplantation can be an important complication of renal transplantation [19]. New-onset diabetes influences allograft survival and has an impact on renal function and increased cardiovascular risk, leading to patient survival [20-22]. In a prospective study, the 12-year graft survival rate was 70% in the non-diabetic control group and 48% in those

developing new-onset diabetes [32]. In our study, diabetes mellitus, which was present before renal transplantation, was found to have a trend for association with rejection.

In a study about 13881 primary renal transplant recipients, low after dialysis diastolic blood pressure and low pre dialysis diastolic blood pressure were associated with decreased risk of death, whereas high diastolic blood pressure after dialysis was associated with increased risk of death. Low blood pressure before transplantation was also associated with decreased risk of graft failure [23]. In our patients, it was shown that the factors affecting the rejection of the graft kidney did not include the pre-transplant hypertension. This may be due to the small number of patients.

Acute rejection of both cellular and humoral type may lead to long-term changes due to reduced graft survival [25-28]. Acute rejection findings of both cellular and humoral types were observed in our patients. Humoral antibody was positive in 2 of 8 patients with acute rejection.

Compared with patients without acute rejection, those with acute rejection at 1 year were more frequently observed in patients with a greater number of HLA mismatch [29]. In our study, no correlation was found between HLA compliance and rejection rate. However, we found that PRA positivity is correlated with acute graft rejection.

It has been found that decreased early graft function after kidney transplantation from live donors reduces graft survival without rejection. However, its effect on graft survival in the long term is not clear. Decreased early graft function is defined as delayed or slow graft function. Weight gain, pre-transplantation dialysis treatment and warm ischemia have been identified as risk factors for the emergence of decreased early graft function. Decreased early graft function also showed negative effects on long-term graft survival [30]. In our patients, BMI of the recipient, pre-transplantation dialysis treatment and duration of warm ischemia were not significantly different in terms of rejection.

High serum PTH levels in both pre-transplantation and post-transplantation were associated with decreased graft function. Roodnat and colleagues in the study of 407 renal recipients in terms of total graft survival when evaluated in terms of high pre-transplantation PTH level was found to be a linear relationship between graft failures [33]. In our study, a positive correlation was found with higher level of PTH in the pre-transplantation period with acute graft rejection.

In conclusion, we found that pre-transplantation PRA positivity and post-transplantation parathyroid hormone levels increased the probability of rejection. The effect of the presence of diabetes mellitus on the development of rejection was limited. Therefore, we suggest that strictly following-up PRA and parathyroid hormone levels in renal transplant recipients.

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Ethical statement: *The study was conducted in accordance with the ethical approval of the University Ethics Committee (Decision number: 29032017-4).*

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