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Factors Influencing Survival and Graft Function of Living Related Kidney Graft Recipients

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In the last two decades there has been remarkable discrepancy between the growing number of dialysis patients and the rate at which kidney transplantations are being performed. The gap between the supply of available kidneys and the demand for them has been progressively increasing (1, 2). As a consequence, donor selection criteria have expanded to include non-heart beating donors and donors of advanced age (1). In addition, the lack of cadaveric organs for transplantation has resulted in an increased number of kidney transplants from living donors. Living kidney transplantation is associated with longer graft and patient survival as compared with cadaveric one. It is an elective operation, and kidneys are obtained after careful screening and less complications of organ procurement and preservation. Nevertheless, numerous studies showed that graft function and survival was affected by different donor non-immunological factors, such as donor age, gender, race, size, mode of death (1, 2, 3, 4).

A lack of cadaveric kidneys has resulted in an increase in living related kidney transplantations at the Institute of Urology and Nephrology in Beograd that presented 70% of all kidney transplantation. Since vast majority of our patients are adults, almost 40% of their donors are older than 60, and among them 30 % are more then 70 years old. That directed us to evaluate the influence of donor factors to long-term transplantation results in our center.

In order to analyzed the influence of donor age to graft function and survival, two recipient groups were compared: group 1 consisting of 115 patients who received a graft from donors older than 60 years (donor age 60 to 85 years), and group 2 consisting of 158 patients who received a graft from donors less than 60 years old (donor age 34 to 59 years). Our analysis shows that donor age has a detrimental effect on short and long-term renal allograft function and survival.

Older grafts from group 1 had significantly poorer survival than grafts from group 2 during the entire studied period (p= 0.001). Graft survival was 88.6%, 79.5%, 71%, 63.3% and 55.8% for group 1 (half-life 84 months) and 97%, 89%, 82.6%, 78.3% and 71.3% for group 2 (half-life 120 months) for every year, when a patient's death was counted as graft loss. Graft survival censored for patient death was 91.2%, 82.7%, 75.8, 70.5 and 63.4% for group 1 (half-life 96 months) and 97.4, 90.7, 84.4, 81.4 and 75.7 % for group 2 (half-life 168 months) for every year, and the difference was statistically significant from the second posttransplant year (p= 0.02-0.004). The difference between donor and recipient age was found to be a significant risk factor for graft survival. In addition, patients with AR episodes had a 1.5 times higher risk for graft loss than patients without AR.

Graft survival was also calculated considering the presence of AR. Inside both studied groups, grafts which experienced AR survived less than grafts without AR and the difference was significant (p= 0.016 for group 1 and p= 0.025 for group 2). Thus, the half-life for grafts from group 1 with AR was 60 months, but 108 months for grafts with no AR. For grafts from group 2 the half-life with and without AR was 80 and 129 months, respectively. Furthermore, the older grafts from group 1 with AR had a significantly shorter survival time than grafts from group 2 with AR (p= 0.019). In the absence of AR the outcome for older and younger grafts was similar (p= 0.07). Namely, AR episodes markedly diminished graft survival of both older and younger kidney grafts but in the absence of AR, survival of older and younger grafts was similar.

Donor age significantly predicted long-term recipient survival i.e. the older the donor kidney the worse the recipient survival. Patient survival for the first five posttransplant years was 98%, 94%, 89%, 82% and 82% for group 1 and 99%, 98%, 98%, 97% and 93% for group 2. A significant difference was observed from the second posttransplant year until the end of the studied period (p= 0.002). This could be partly due to recipient age, because our recipients, being mostly children of older kidney donors, were significantly older than the recipients of younger kidneys. In addition they were longer on hemodialysis before transplantation. Both conditions have already been reported to be associated with higher co-morbidity in patients on hemodialysis (5). Additionally, the Cox proportional hazard model revealed that the high risk factor for patient death was independently associated with increase of donor age (p= 0.01), polycystic kidney disease as an underlying kidney disease (p= 0.004) and graft function (p= 0.0000). The latter implied that a high serum creatinine level was followed by a poor patient outcome.

Data obtained indicated that donor age affected not only graft survival but also graft function and both had a significant influence on recipient survival. The analysis of factors influencing graft function (Table 1) revealed that donor age and the age difference between donors and recipients were the most significant risk factors modifying graft function in the first post-transplant year in both groups.

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Table 1. Risk factors for high serum creatinine level at different points of the follow-up period in group 1 (receiving graft from older donor) and group 2 (receiving graft from younger donor)

Month after Tx	Group 1			Group 2		
	Risk factors	β	p	Risk factors	β	p
6	Donor age	0.213	0.033	SGF Recipient gender Donor age	0.415 -0.193 0.157	0.000 0.008 0.029
9	Acute rejection HLA A MM HLA B MM Donor age HD, month	0.309 -0.211 -0.210 0.301 -0.220	0.001 0.029 0.034 0.002 0.020	SGF Recipient gender D-R age difference	0.365 -0.233 0.198	0.000 0.003 0.011
12	D-R age difference Acute rejection PRA	0.349 0.294 -0.197	0.000 0.002 0.035	SGF D-R age difference	0.313 0.202	0.000 0.010
24	Acute rejection HLA A MM Recipient gender D-R gender difference	0.274 0.230 -0.269 0.320	0.01 0.032 0.04 0.039	SGF D-R age difference D-R gender difference PRA	0.297 0.223 -0.276 0.275	0.001 0.009 0.03 0.01

D-donor, R-recipient, HLA A MM-mismatches in HLA A and B, SGF- slow graft function

Later on, i.e. after the second posttransplant year, donor age disappeared from the risk factors affecting graft function, but the other risk factors differed between the two groups. In recipients of older grafts immunological factors (HLA mismatches, PRA titer, acute rejection) had the greatest influence on graft function. In contrast to this, graft function in younger graft recipients was predominantly affected by non-immunological factors (male gender, slow graft function). Although slow graft function was the main risk factor for poorer younger graft function, its influence on older graft function could not be disregarded, particularly due to the significantly higher incidence of slow graft function after transplantation of old grafts. The multivariate analysis indicated that donor age was a risk factor for slow graft function (p=0.002), while HLA B-mismatches significantly increased the risk factor for acute rejection (p=0.03).

A high incidence of slow graft function including delayed graft function in older grafts as well as its negative effect on graft function and outcome has been reported elsewhere in other series (6, 7). There is also evidence that slow graft function strongly predisposed to acute rejection which was found to be a significant risk factor for both graft function and graft survival, especially for older kidney grafts. Nevertheless, acute rejection occurred at a similar rate in both our groups but this is not a solitary result. Thus, some authors reported a similar incidence of AR in recipients of older and younger kidneys (6) while others found AR more frequently in older donor kidney recipients (7). Regardless of its frequency, AR was shown to be one of the main risk factors for graft function and survival (8, 9). Moreover, Matas et al. identified AR as the only significant risk factor for late graft failure in a group of living graft transplantations. In our study chronic renal allograft dysfunction, irrespective of its cause, started earlier in recipients of older kidneys and in the first posttransplant year its frequency was significantly higher in this group than in the recipients of younger kidneys. This might be related to a higher proportion of slow graft function as well as acute rejection which did not resolve with fully functional recovery in older grafts.

In spite of major improvements in immunosuppression, renal grafts continue to fail due to influence of numerous immunologic and non-immunologic factors. Recently, it was suggested that the strategies for improvement baseline graft function, defined as glomerular filtration rate (GFR) at post-transplant month 6, might be more important for graft outcome than strategies for slowing decline of GFR (10). Although the recipient of a living donor graft is more likely to receive a kidney with good functional reserve, the lowest acceptable level of GFR was not defined neither with respect to donor safety nor considering the recipient benefit. As the graft function at the end of the early post-transplant period depends on quality of transplanted kidney and early post-transplant events (11), we decided to analyze the transplantation outcome of living related donor grafts which avoided acute rejection and delayed graft function. In order to evaluate the influence of donor single kidney glomerular filtration rate (SKGFR), designed as the baseline graft function, on patients and grafts survival as well as on the change of graft function over time, the factors not primarily determined by donor kidney were excluded, meaning patients with delayed graft function and acute rejection were excluded from the additional analysis. From the previous studied group, 70 recipients, finally selected for analysis, were divided into two groups according to the baseline graft function: *group 1,* receiving kidney with SKGFR less of 50 ml/min (32 patients), and *group 2,* receiving kidney with SKGFR equal or above 50 ml/min (38 patients). Although the global kidney function of all donors in our analysis was normal, relative contribution of the kidney planned to be transplanted to overall GFR (SKGFR) widely varied from 25 to 95 ml/min before donation. Despite these variations in GFR it seems

that the living related transplantation was safe both for donors and for recipients.

Results obtained after univariate and multivariate analysis confirmed that graft function does not strongly depend on the functional kidney mass transplanted (4). The baseline graft function, that means GFR of kidney planed to be transplanted, was not proved to be of influence on post-transplant graft function regardless of whether it was measured at different points of post-transplant period or expressed as the change of creatinine clearance (CCr) over the time (Table 2).

Table 2. Variables associated with the rate of graft function change

	Standardized coefficients β	p-value
Recipient gender	0.360	0.003
Donor gender	0.280	0.007
CCr 6 months	--0.655	0.000
CCr 2 years	0.627	0.000

However, significant relationship was found between the graft function at particular points of post-transplant period and graft function change rate. So, negative influence of CCr measured at 6 months on the rate of CCr change was found. While Gourishankar et al. (12) found no increase in the rate of CCr decline for grafts that had lower 6-month CCr, our results showed that higher 6-month CCr was related with faster decline of CCr in the subsequent period. Our results indicated faster decline of CCr in patients with higher increase of CCr during the first 6 post-transplant months that was registered in group 1 with lower SKGFR. So, although we could not prove the influence of SKGFR on subsequent graft function, more progressive CCr decline in patients with lower SKGFR and more marked hyperfiltration after transplantation, indicated that SKGFR was not insignificant.

In conclusion, despite worse graft function and poorer patient and graft survival, kidney transplantation from living related older donors may be an acceptable practice especially when wait times are prolonged or access to dialysis limited

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