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ANALYSIS OF RECIPIENT AND GRAFT SURVIVAL AFTER PRIMARY AND SECOND KIDNEY TRANSPLANTATION

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Objective: to evaluate the 1- and 5-year graft and recipient survival after primary and second kidney transplantation, to compare the outcomes depending on the age of recipients. **Material and methods.** The treatment outcomes for 364 patients who underwent kidney transplantation at Sklifosovsky Research Institute of Emergency Care, Moscow over the period from 2007 to 2019. Of these, 213 patients underwent kidney transplantation for the first time, while 151 patients were having a second transplantation. We analyzed the effect of previous transplants, as well as the age of the recipients on long-term survival rates. **Results.** No significant difference in 1- and 5-year survival of kidney recipients after primary and second transplantations was found. In contrast, the long-term graft survival significantly depended on this criterion and turned out to be significantly higher after primary transplantations. The 1- and 5-year survival of older recipients was lower than the survival of younger recipients after primary and second kidney transplantation. The 1-year graft survival after primary kidney transplantation was higher in young recipients than in older recipients of the same group, however, but there were no significant differences in the 5-year graft survival. After second transplantations, there were no significant differences in the 1- and 5-year graft survival depending on the age of recipients. **Conclusion.** A history of previous transplantation is an important factor in kidney transplantation outcome, which must be taken into account in clinical practice.

Keywords: primary kidney transplantation, second kidney transplantation, outcomes, recipient survival, kidney graft survival.

INTRODUCTION

Most experts believe that a second kidney transplant significantly affects the survival rate of renal allografts (RA). However, reports on studies carried out in this direction are often contradictory. According to the Collaborative Transplant Study (CTS) of the University of Heidelberg, carried out from 1990 to 2018, the 1-year survival rate of RA after primary and second kidney transplants was 90% and 85%, respectively; the 5-year survival was 76% and 70%, respectively [1]. Pour-Reza-Gholi et al. analyzed the results of 2,150 kidney transplants, 103 of which were second transplant surgeries. The 1-, 2-, 3-, and 5-year graft survival rates in patients who underwent primary transplantation were significantly higher than in patients who did second transplantations (92.9%, 91.5%, 89.8%, 85.3% and 81.4%, 78.9% , 78.9%, 73.7%, respectively (P = 0.0037). No significant differences in recipient survival were noted by the researchers (P = 0.63) [2].

Conflicting data has been published in the Australian and New Zealand registry ANZDATA for the period of 2011 to 2018. For primary and second kidney transplants, 1-year recipient survival was 96% and 99%, while 5-year recipient survival was 88% and 93%. The 1-year survival rate of RA also did not differ significantly (94% and 97%, respectively), while the 5-year survival rate was 75% and 85%, respectively [3]. Jędrzejko et al. analyzed the treatment outcomes of 406 patients who underwent kidney transplantation from 2013 to 2015, and obtained similar results. First transplantation had no significant effect on RA and recipient survival [4]. Ingsathit and colleagues analyzed data from Thailand's transplant registry, looking at the outcomes of 3,337 transplants performed between 1993 and 2011. There were no statistically significant differences in 1-, 5-, and 10-year RA and recipient survival rates in the primary and repeat kidney transplant groups (P = 0.63 and P = 0.42, respectively) [5]. Similar results were published by Korean scientists (Sang Hyup Han et al.). They analyzed the outcomes of 3,000 patients who underwent kidney transplantation from 1969 to 2018, of which 201 cases were repeat kidney transplants. Patient and death-censored graft survival for primary and repeat transplantation did not differ (P = 0.684 and P = 0.564, respectively) [6]. Heldal et al. analyzed the outco-

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mes of 733 kidney transplants in recipients over 65 years of age. In 687 cases, the transplants were primary, and in 46, they were repeats. The 5-year death-censored and death-uncensored graft survival did not differ between the groups (P = 0.789 and P = 0.475, respectively) [7].

In Eurotransplant, a large multicenter retrospective study, it was observed that primary non-function had a higher incidence after a second kidney transplantation than after a primary transplantation (12.7% and 7.1%, respectively, P < 0.001) [8]. There were no statistically significant differences in recipient survival after primary and second kidney transplant surgeries (P = 0.532). However, the 5-year death-censored graft survival was significantly higher after primary transplantation (89% and 85%, P < 0.001) [9].

A study published by Puneet Sood et al. found no significant effect of prior transplantation on 1- and 5-year censored and uncensored graft survival (P = 0.70) [10]. In contrast, the group of recipients who underwent primary kidney transplantation had better 1- and 5-year survival compared with the group of patients who had a second kidney transplantation (P = 0.013) [11].

Objective: to evaluate the 1- and 5-year graft and recipient survival after primary and second kidney transplantation, and to compare the outcomes depending on the age of recipients.

MATERIAL AND METHODS

The study was based on a retrospective analysis of the results of 364 kidney transplants performed at Sklifosovsky Research Institute of Emergency Care in Moscow, from 2007 to 2019. The inclusion criterion was primary and repeated (second) kidney transplantation from a deceased donor. The exclusion criterion was combined kidney transplantation and transplantation of other organs from a living related donor. The patients were divided into groups – those that have had only primary transplantation and those with a second transplantation.

Follow-up period: from the time of kidney transplant surgery until loss of RA function or recipient death – completed follow-up; in case of loss of communication with the recipient – a censored follow-up.

Study: To assess the recipient and graft survival rate, we used data from the medical records of patients at the kidney transplantation department of Sklifosovsky Research Institute of Emergency Care, and out-patient medical records of RA recipients of the Moscow City Scientific and Practical Center for Nephrology and Transplant Kidney Pathology.

Study groups: The first comparison group, formed by stratified sampling by recipient gender and age, quality of donor organ (standard donor or expanded criteria donor), consisted of 213 RA recipients out of 1316 recipients with primary kidney transplantation. The second study group consisted of 151 recipients who underwent a second kidney transplantation.

Table 1

Main characteristics of patients after the first and second kidney transplantation

Recipients, n	All (n = 364)	Group 1 (n = 213)	Group 2 (n = 151)	P
Age, m (25–75%), years	45 (35; 54)	46 (36; 54)	44 (34; 54)	0.45
Age range, years	18–72	18–72	20–71	
Male, % (n)	57.4 (209)	60.6 (129)	53 (80)	0.25
Female, % (n)	42.6 (155)	39.4 (84)	47 (71)	
BMI, m (25–75%), kg/m^2	24.1 (21.2; 27.7)	24.6 (21.6; 28.2)	23.9 (21.1; 27.1)	0.12
Sensitized, % (n)	45.1 (134)	21.3 (35)*	74.4 (99)*	0.000
No data, % (n)	18.4 (67)	23.0 (49)	11.9 (18)	

* patients with no data were excluded from the estimation.

Recipients of both groups did not differ significantly in gender, age, and body mass index (Table 1). A significant difference between the groups was found in the number of patients sensitized to the major histocompatibility complex (HLA) (P = 0.000). Thus, HLA antibodies were found in a greater number of patients with repeated kidney transplantation in comparison with patients who had not had any previous transplantation.

Among the diseases leading to end-stage kidney disease, chronic glomerulonephritis (44.8%, n = 163) and chronic pyelonephritis (16.8%, n = 61) were most common in RA recipients in both groups. The latter – both as an independent disease, and as a complication of congenital anomalies of the urinary system and kidney stone. However, a comparative assessment of the disease pattern between the groups revealed differences (P = 0.00028). Specifically, there were significantly fewer patients with polycystic kidney disease, diabetes mellitus, and hypertension among the repeat transplant recipients (Fig. 1).

In the study groups, there were no significant differences in the characteristics of donor organs (Table 2).

To assess recipient and kidney graft survival rates, depending on age, groups 1 and 2 patients were considered in subgroups. The subgroups were divided by age as follows: from 18 to 49 years old (young recipients) and from 50 to 72 years old (older recipients) (Table 3).

Immunosuppressive therapy: patients in both groups received a three-component immunosuppressive therapy (calcineurin inhibitors + inosine monophosphate dehydrogenase/proliferative signal inhibitors + corticosteroids (100% of recipients in both groups). In order to prevent acute rejection, 84.1% of recipients received induction

with chimeric monoclonal antibodies – antagonists of CD-25 antigen or lymphocyte-depleting antibodies (antithymocyte immunoglobulin) (Table 4).

There were statistically significant differences in the used induction component and the basic immunosuppressive agent in the recipients of the study groups. Specifically, group 2 recipients with a high immunological risk received a more aggressive immunosuppressive therapy: 92.7% of patients received tacrolimus, and 62.9% received induction with lymphocyte-depleting antibodies. These drugs were used reliably less often in group 1 patients with a low immunological risk.

The data obtained was *statistically analyzed* using the Statistica for Windows v.12.0 software package, StatSoft Inc. (USA). Normality of distribution was assessed by the Shapiro–Wilk test. Mann–Whitney U test, Fisher's exact test (two-sided), chi-squared test for four-field and arbitrary tables were used to compare groups. The value $P < 0.05$ was considered statistically significant. The Kaplan–Meier estimator was used to analyze the survival rate. Survival across groups was compared using a log-rank test. Confidence intervals for survival were considered according to Weibull. Survival curves were calculated from the date of surgical treatment.

RESULTS AND DISCUSSION

Analysis of recipient survival after primary and second transplantations revealed no significant differences. Specifically, the 1-year recipient survival rate in group 1 and group 2 was 98% (95% CI 97–99) and 97% (95%

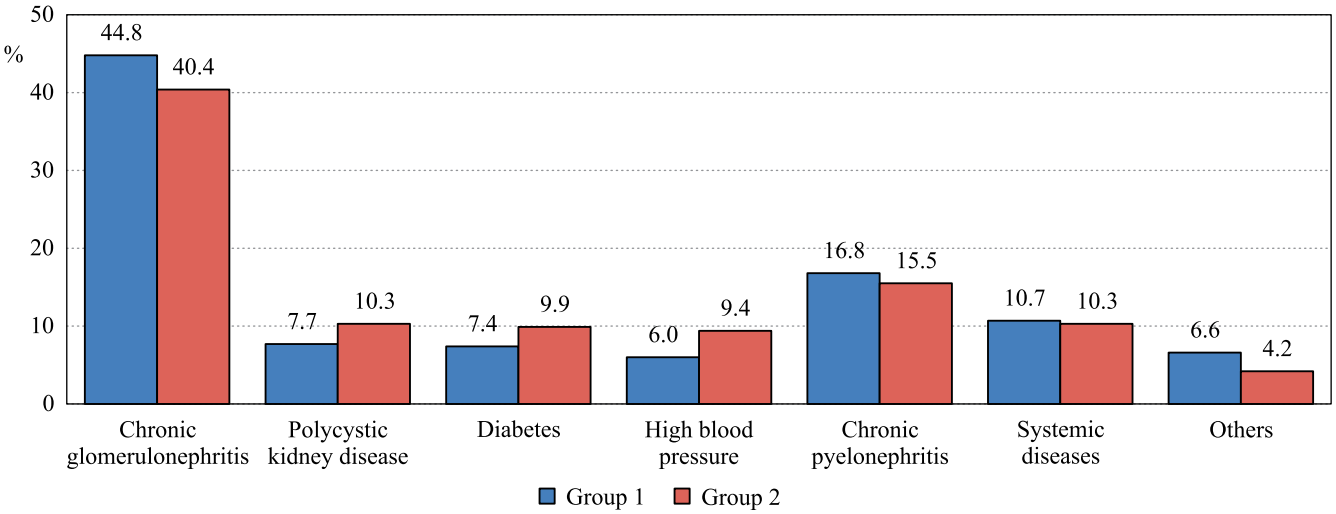

Fig. 1. Diseases that led to end-stage chronic renal failure in kidney graft recipients

Table 2

Donor characteristics

Renal allograft, n	All (n = 364)	Group 1 (n = 213)	Group 2 (n = 151)	P
Donor gender: Make, % (n) Female, % (n) No data, % (n)	 63.7 (232) 28.6 (104) 7.7 (28)	 62.0 (132) 29.1 (62) 8.9 (19)	 66.2 (100) 27.8 (42) 6 (9)	0.11
Donor's age, years: m, (25–75%) Age range No data, % (n)	 47 (38; 54) 18–69 (26)	 47 (39; 53) 18–69 (18)	 46 (34; 55) 20–67 (8)	0.38
Donor criteria: Standard, % (n) Extended, % (n) No data, % (n)	 64.8 (236) 28.3 (103) 6.9 (25)	 62.9 (134) 29.1 (62) 8 (17)	 67.5 (102) 27.2 (41) 5.3 (8)	0.06
Renal allograft preservation, hours: m, (25–75%) No data, % (n)	 13 (11; 16) (5)	 13 (11; 16) (2)	 14 (11.3; 16) (3)	0.36
HLA incompatibility: m, (25–75%) No data, % (n)	 4 (3; 4) 2.2 (8)	 4 (3; 5) 2.8 (6)	 4 (3; 4) 1.3 (2)	0.55

CI 94–98), respectively, (P = 0.06). Their 5-year survival rate was 98% (95% CI 95–99) and 93% (95% CI 89–96), respectively (P = 0.23) (Fig. 2).

Thus, our results confirm that there are no statistically significant differences in the 1- and 5-year survival rates of recipients after primary and repeated kidney transplantation, and are consistent with similar survival rates of RA recipients in the world.

Analysis of the renal graft survival in recipients of the study groups found statistically significant differences. Specifically, the 1-year graft survival in group 1 and group 2 was 97% (95% CI 95–99) and 88% (95% CI 84–92), respectively (P = 0.0027). The 5-year RA survival in the study groups was 90% (95% CI 86–93) and 75% (95% CI 68–80), respectively (P = 0.0048) (Fig. 3).

It should be noted that only 1.4% (n = 3) of group 1 recipients had a primary nonfunction, whereas in group 2 recipients, such an outcome was observed in 7.9% (n = 12) of cases (P = 0.002).

Our study comparing 1- and 5-year renal graft survival after primary and second transplantation, showed a significant difference in long-term survival and confirmed previously published data from the University of Heidelberg and Pour-Reza-Gholi et al. The high incidence of primary non-function after a second kidney transplantation was also confirmed, although according to our observations, it turned out to be lower than in the Eurotransplant study.

Table 3

Distribution of renal allograft recipients of the studied groups into subgroups

Groups	1		2	
Subgroups	1.1	1.2	2.1	2.2
Age, years	18–49	50–72	18–49	50–71
Recipients %, n	60.6 (129)	39.4 (84)	60.9 (92)	39.1 (59)

Table 4

Immunosuppressive therapy in groups 1 and 2

Number of recipients, n	All (n = 364)	Group 1 (n = 213)	Group 2 (n = 151)	P
Induction:				
Basiliximab, % (n)	47.6 (173)	62 (132)	27.2 (41)	0.000
Lymphocyte-depleting antibodies, % (n)	36.5 (133)	17.8 (38)	62.9 (95)	
No induction, % (n)	15.9 (58)	20.2 (43)	9.9 (15)	
Calcineurin inhibitors:				
Cyclosporine, % (n)	21.4 (78)	31.5 (67)	7.3 (11)	0.000
Tacrolimus, % (n)	78.6 (286)	68.5 (146)	92.7 (140)	
Mycophenolates, % (n)	98.9 (360)	99.5 (212)	98 (148)	0.17
Everolimus, % (n)	1.1 (4)	0.5 (1)	2 (3)	

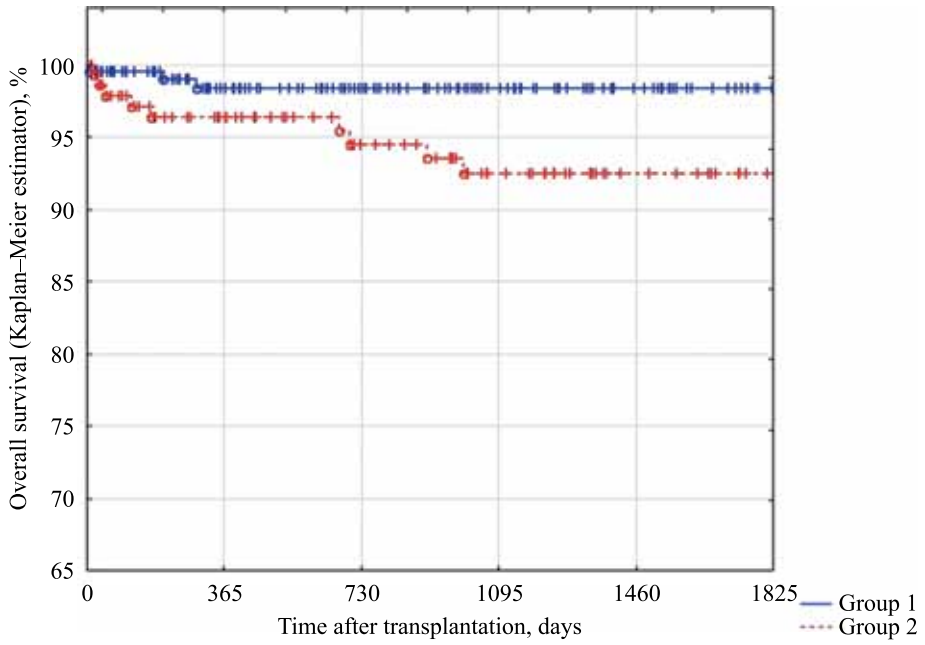

Fig. 2. Kidney recipient survival after primary and second transplantation

The 1- and 5-year survival rates of relatively young recipients in group 1 (subgroup 1.1) were 100%. The 1- and 5-year survival rate of older recipients in this group (subgroup 1.2) was 95% (95% CI 91–98) (Fig. 4).

A comparison of the 1-year 1- and 5-year recipient survival in subgroups 1.1 and 1.2 revealed statistically significant differences (P = 0.024 and P = 0.017). Thus, higher survival rates were found in the subgroup of young recipients after primary transplantation.

The 1-year survival rate for young recipients of group 2 (subgroup 2.1) was 100%, and their 5-year survival rate was 98% (95% CI 96–99). For older recipients (subgroup 2.2), it was 91% (95% CI 84–96) and 82% (95% CI 74–90), respectively (Fig. 5).

A comparison of the 1-year and 5-year recipient survival in subgroups 2.1 and 2.2 of group 2 found statistically significant differences (P = 0.009 and P = 0.001). In both group 1 and group 2 recipients, higher survival rates were observed among younger recipients.

Thus, the survival rate of young recipients in groups 1 and 2 was, as expected, statistically higher than in older

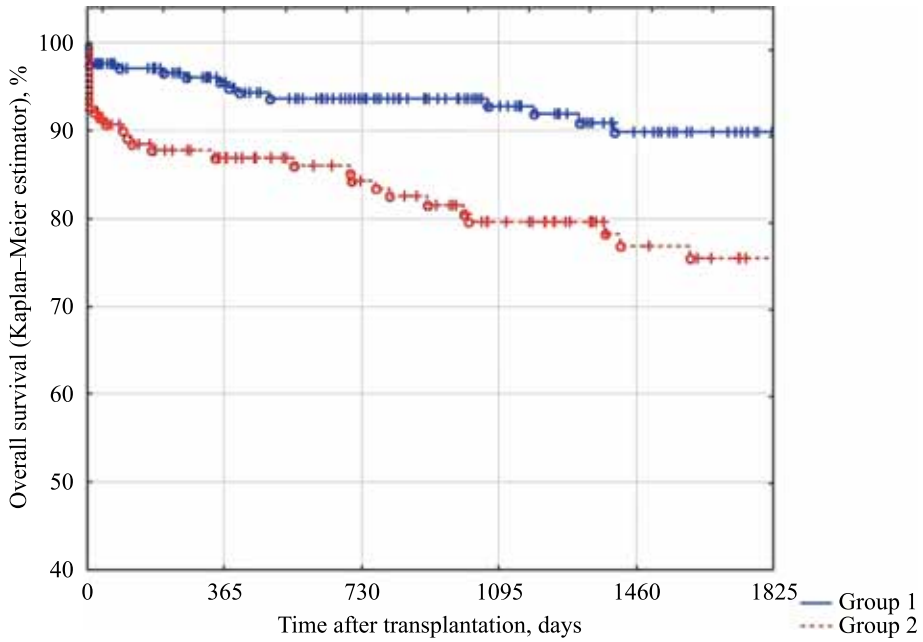

Fig. 3. Graft survival in recipients after primary and second kidney transplantation

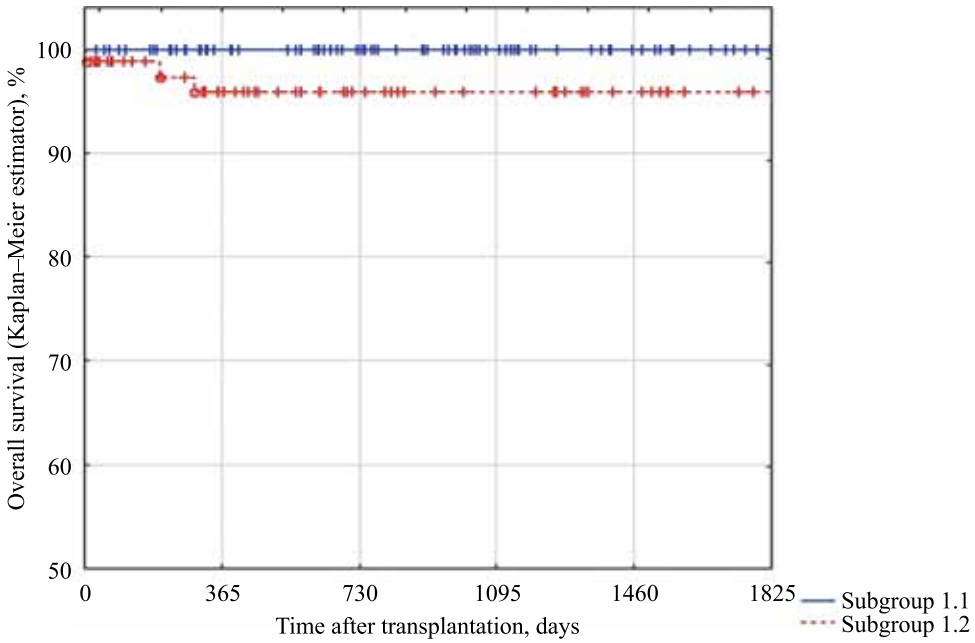

Fig. 4. Recipient survival in group 1 according to patient age

recipients. This distribution is also characteristic of the general population.

The 1-year and 5-year kidney graft survival in young recipients of group 1 was 98% (95% CI 97–99) and 91% (95% CI 87–95), respectively. In older patients in group 1, the RA survival rate was 91% (95% CI 86–96) and 82% (95% CI 75–88), respectively (Fig. 6).

A comparison of the 1-year kidney graft survival in young and older recipients of group 1 (subgroups 1.1 and 2.1) revealed a statistically significant difference (P = 0.006); however, when comparing 5-year survival in these subgroups, no significant differences were observed (P = 0.14), although the RA survival rate remained higher in young recipients.

Perhaps this loss of RA survival advantage in younger recipients is due to the tendency to develop more frequent humoral rejection observed in the early years after transplantation, whereas in elderly recipients, the significance of immunological factors of graft loss is no longer as high.

The 1- and 5-year RA survival in young recipients of group 2 was 91% (95% CI 86–95) and 80% (95%

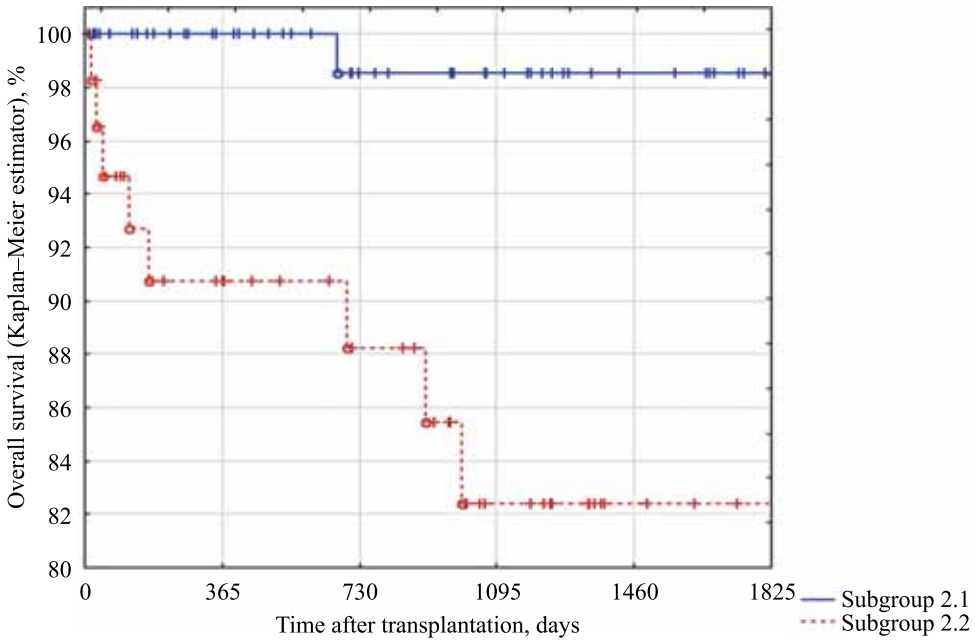

Fig. 5. Recipient survival in group 2 according to patient age

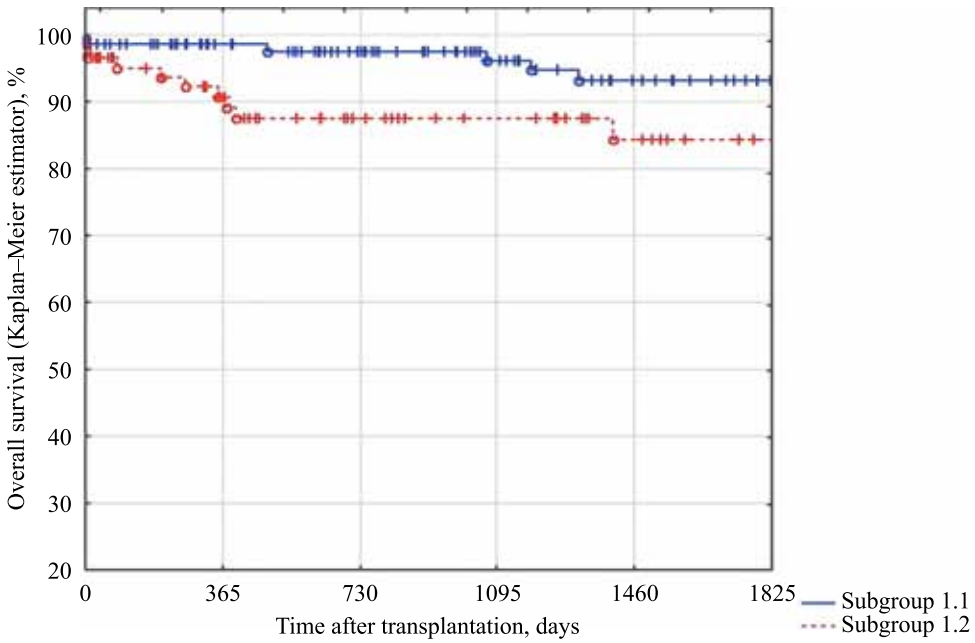

Fig. 6. Graft survival in group 1 recipients depending on age

CI 73–86), respectively. In older recipients, it is 80% (95% CI 72–88) and 70% (95% CI 61–80), respectively (Fig. 7).

A comparison of 1- and 5-year graft survival in recipients of different ages in group 2 (subgroups 2.1 and 2.2) found no statistically significant differences (P = 0.078 and P = 0.17).

The absence of the expected statistical difference in the 5-year RA survival rate in recipients of different age groups is probably due to the influence of factors that are different in nature, but similar in direction. Specifically, the RA loss in young recipients may be predominantly associated with immunological causes leading to graft loss as a result of rejection. Whereas RA loss is more often in older recipients due to primary non-functioning graft or death. This seems logical, taking into account the age-related characteristics of comorbidity and the current clinical practice of organ allocation from age-related and suboptimal donors.

Thus,

1. The 1-year recipient survival after primary and second kidney transplantation in our observations was 98% and 97% (P = 0.06); the 5-year survival was 98% and 93% (P = 0.23), respectively.
2. The 1-year RA survival after primary and second transplantation was 97% and 88% (P = 0.0027), the 5-year survival was 90% and 75% (P = 0.0048), respectively.
3. After primary transplants, the 1-year RA survival rates in subgroups 1.1 and 1.2 were 98% and 91% (P = 0.006), respectively. The 5-year RA survival in these subgroups was not statistically different – 91% and 82% (P = 0.14).
4. The 1-year RA survival in subgroups 2.1 and 2.2 was 91% and 80%, respectively (P = 0.078), 5-year survival rates were 80% and 70% (P = 0.17). After repeated transplantations, there were no significant differences in 1- and 5-year RA survival depending on recipient age.
5. The incidence of primary non-function after primary transplantation and after repeated transplantation was 1.4% and 7.9%, respectively (P = 0.002).

CONCLUSION

The generally accepted opinion that primary transplantation has a negative effect on the outcome of a second one is still being debated among specialists and needs to be confirmed, since data from various transplant centers published in the medical literature are contradictory. Our paper presents a 12-year experience of one Russian transplant center in relation to the outcomes of repeated kidney transplants. We did not find any statistically significant difference in the 1- and 5-year recipient survival rates after primary and repeated kidney transplants. On the other hand, graft survival after primary transplant was significantly higher than after the second transplant. In addition, primary non-function was significantly more frequent after repeated transplantations. At the same time, recipient survival in the older age group was naturally significantly lower than with younger recipients, both after primary and after repeated transplantation. A comparison of the 1-year survival of primary renal transplants showed it to be significantly higher in the subgroup of young recipients. However, a comparison of the 5-year survival of primary kidney transplants no longer revealed any statistically significant difference,

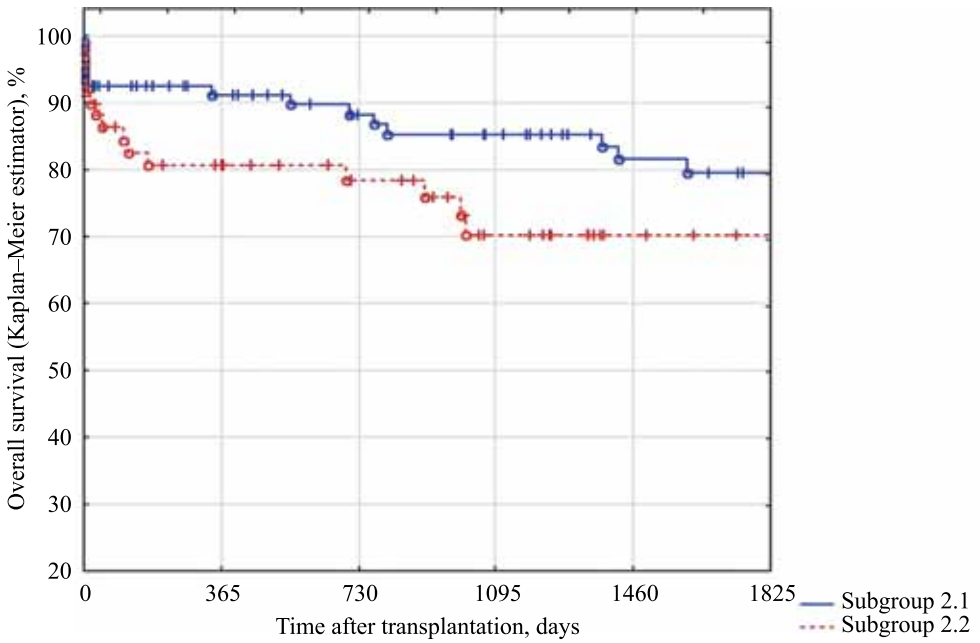

Fig. 7. Graft survival in group 2 recipients depending on age

apparently due to the activity of immunological factors of graft loss in young recipients. When comparing 1- and 5-year survival rates for repeated grafts depending on recipient age, significant and clinically significant differences were evident, which is clearly shown in Fig. 7, but their reliability has not been statistically confirmed.

The authors declare no conflict of interest.

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