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Transplantation of expanded criteria kidney grafts to elderly recipients in the Sklifosovsky Research Institute for Emergency Medicine

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Introduction. *The expansion of the criteria for donor organ retrieval contributes to an increase in the number of kidney transplantations to elderly recipients; but in view of reduced requirements to donor organ quality, a further analysis of transplantation outcomes is needed.*

The aim *was to analyze and compare the outcomes of kidney transplantation to elderly patients depending on the donor organ quality.*

Material and methods. *The study was based on the analysis of the kidney transplantation outcomes in 61 elderly recipients, including 51 transplantations performed from expanded criteria donors (group 1), and other 10 from standard donors (group 2). Based on clinical, laboratory, histological, and instrumental diagnostic data, we compared the graft function recovery rates, graft/recipient survival rates, the causes of graft loss in the early posttransplant period.*

Results. *Patients of group I had significantly higher delayed graft function rates (37.3% vs. 10%), graft non-function rates (15.7% vs. 0%), and lower early posttransplant survival rates (72.5% vs. 100%). Graft function recovery rate was 58.8% in group I, and 100% in the patients of group II. The most common cause of the graft loss and the renal graft removals performed in the early posttransplant period was the poor graft quality due to the donor's existing pathology.*

Conclusion. *The study demonstrated a statistically significant deterioration of the initial graft function, significantly increased graft non-function rates, and decreased graft survival rates in the early posttransplant period in the elderly recipients after kidney transplantation from expanded criteria donors.*

Keywords: kidney transplantation, kidney graft non-function, kidney graft from expanded criteria donor, kidney graft quality

CKD, chronic kidney disease

CVA, acute cerebrovascular accident

DM2, type 2 diabetes mellitus

GFR, glomerular filtration rate

HD, hypertension disease

HLA, human leukocyte antigen

KT, kidney transplantation

MCCOD, Moscow Coordination Center for Organ Donation

PGNF, primary graft non-function

PIRAG, primarily infected renal allograft

RAG, renal allograft

TBI, traumatic brain injury

WLKT, waiting list for kidney transplantation

Introduction

In recent years, the number of kidney transplants performed in the Sklifosovsky Research Institute for Emergency Medicine has progressively increased: from 80-95 annual operations to 190 or more thanks both to the improvement in the activities of the organ donation service in the capital and the gradual expansion of donor organ suitability criteria for transplantation, which led to an increased pool of potential donors and the number of organ removals. However, it is necessary to realize that the transplant activity has largely been growing due to the increased number of suboptimal organ transplantations, i.e. the kidneys harvested from donors with the characteristics far from ideal. In the opinion of most foreign authors, the expanded criteria donors (ECDs) include those over 60 years old or at the age of 50-59 years with at least 2 of the 3 criteria listed below [1, 2]:

- Hypertension disease (HD);
- Acute cerebrovascular accident as the cause of death;
- Increased serum creatinine levels (over 1.5 mg/dL –132.7 μmol/L).

Russian transplantologists also consider the following donors as ECDs (also referred to as suboptimal or marginal donors) [3]:

- Those with the history of type 2 diabetes mellitus (DM2);
- Those with traumatic brain injury (TBI) complicated by traumatic or hemorrhagic shock as the cause of death;

- Those on high doses of drugs to support cardiac function (dopamine over 15 mcg/kg/min, norepinephrine over 1000 ng/kg/min or phenylephrine and epinephrine in a standard dose).

Donors after cardiopulmonary death (asystolic donors whose death occurred due to irreversible circulatory arrest) can be either ECDs or standard donors [1].

It is known that, besides the recipient-derived factors, such as HLA incompatibility, pre-existing sensitization, age, race, obesity [4, 5], the initial quality of renal allograft (RAG) is rather important for its function recovery. And such a crucial criteria as the donor elderly age naturally increases the incidence of dysfunction and worsens the prognosis for the RAG survival both in the early and long term after transplantation [6-11]. In addition, the donor-derived factors affecting the graft recovery and survival and defined as the "organ quality" include the graft size, the history of arterial hypertension, diabetes, renal failure, prolonged hypotension in the agony period [12], the cause of death, and the cold ischemia time [13]. Thus, the 1-year and 5-year graft survival rates make 92% and 70% for renal grafts from standard donors, and 80% and 44% for renal grafts from ECDs, respectively [1, 14].

The serum creatinine level after kidney transplantation (KT) is an important prognostic criterion for long-term graft survival [15]. The transplanted kidney function is considered satisfactory if the serum creatinine level has stabilized at lower than 200 μg/mL, the graft function is considered good at lower than 150 μmol/L with a glomerular filtration rate (GFR) of over 40 ml/min [16].

Patients older 60 years account for 9-13% of the total number of potential recipients on the waiting list for kidney transplantation (WLKT) in

the Sklifosovsky Research Institute for Emergency Medicine, which is slightly lower than in Europe and the United States. Due to an earlier diagnosis of chronic kidney disease (CKD), an improved treatment quality for such patients by using dialysis techniques and renal replacement therapy and, consequently, and their increased life span, the RAG recipients' return for repeated transplantation, the probability of the increase in the number of elderly patients on WLKT in future is high. According to the American Registry of kidney transplant recipients, from 2006 to 2009, the greatest increase was observed in the group of 50-64-year-old patients (up to 41.1%), and now there is an increase in the number of recipients over 65 years old (up to 16.7%) [17, 18]. Taking into account the age and the system of renal graft allocation in Moscow, the kidney transplantation from ECDs will be the most probable option for elderly patients.

Thus, the assessment of kidney transplantation outcomes from suboptimal donors to recipients older 60 years is currently extremely crucial.

The aim was to analyze and compare the kidney transplantation outcomes in elderly patients with respect to the donor organ quality.

Material and methods

Study groups

The study was based on a retrospective review of renal allotransplantation from posthumous donors performed to patients over 60 years old in the Sklifosovsky Research Institute for Emergency Medicine. From January 2015 to June 2017, 61 KTs were performed in elderly recipients. The criteria for inclusion in the study were the recipient's age over 60 years old, the blood group compatibility with the donor, the negative lymphocytotoxic test. The criterion for group allocation was the donor organ

quality (standard vs. suboptimal i.e. from ECDs). The RAG quality assessment was made basing on the organ passport data. The donor subopimality was defined according to the criteria recognized world-wide. The kidney graft was allocated to a specific patient on WLKT, as determined by the Moscow Coordination Center for Organ Donation (MCCOD) considering the histocompatibility degree, matching by age, the waiting time, without taking into account individual recipient's characteristics (anthropometric data, secondary adrenal insufficiency, the presence of severe arterial hypotension, concomitant diseases, and donor-specific antibodies). Preliminary "time-zero" RAG biopsy was not routinely performed. No recipient older 60 years was excluded from the study.

Fifty one kidney transplantations from ECDs were performed to 48 elderly recipients. The different numbers of donor organs and recipients were due to the number of replacement transplantations (n=3), i.e. repeated transplantations at one and the same hospitalization period that were performed with the removal of the initially transplanted graft and its replacement with a new graft. All those recipients comprised the study group. The comparison group was represented by elderly patients (n = 10) who underwent KT from standard donors (n = 10) over the same period of time (Table 1).

Table 1. Characteristics of recipient groups

Number of recipients, n	1st group (Study group) 48	2nd group (Comparison group) 10	P
Donor gender: male,% (n) female,% (n)	 47.9 (23) 25 (52.1)	 40 (4) 60 (6)	0.510
Age, years, Me (25-75%)	63.5 (61.5; 67.5)	62 (60; 66)	0.241

Mean arterial pressure, mmHg, Me (25-75%) (min, max)	140 (130; 150) 90-190	140 (140; 160) 130-160	0.937
Pre-existing Anti-HLA antibody content > 500 IU,% (n)	25 (12)	40 (4)	0.439
Underlying disease that caused CKD			
Chronic glomerulonephritis,% (n)	22.9 (11)	10 (1)	0.669
Polycystic kidney disease,% (n)	22.9 (11)	30 (3)	0.690
DM2,% (n)	8.3 (4)	10 (1)	1,000
Hypertension disease,% (n)	8.3 (4)	10 (1)	1,000
Hypertension disease + DM2,% (n)	4.2 (2)	0	1,000
Chronic pyelonephritis,% (n)	8.3 (4)	20 (2)	0.273
Systemic diseases,% (n)	6.3 (3)	20 (2)	0.201
Other,% (n)	18.8 (9)	0 (0)	0.334

There were no statistically significant differences between the recipients of two groups in demographic characteristics, the systolic blood pressure level, the pre-existing anti-HLA antibody content, and the CKD etiology.

The differences between the kidney recipients in donor-derived factors were statistically significant and served the basis for patient allocation into groups. Thus, the Study group patients were those who received KT from donors with the suboptimal criteria that are listed in Table 2.

Table 2. Donor-associated criteria for recipient allocation to the Study group

Criteria	Number
Kidney transplant, n	51
Asystolic donor, % (n)	7.8 (4)
Donor older 60 years of age, % (n)	27.5 (14)
Donor aged 50-59 years old with death from cerebrovascular causes, % (n)	60.8 (31)
Donor with TBI complicated by hemorrhagic shock, % (n)	3.9 (2)
Donor with blood creatinine higher 150 μmol/L, % (n)	17.6 (9)
Persistent arterial hypertension in the donor, % (n)	33.3 (17)
High level of inotropic support at the time of organ retrieval*,% (n)	68.6 (35)

* When using a single drug: dopamine dose over 15 μg/kg/min or norepinephrine dose over 1000 ng/kg/min; or phenylephrine and epinephrine in a standard dosage; or using a combination of two drugs.

In 90.2 % of cases (n = 46), the donor had from 2 to 4 suboptimality criteria.

When assessing the donor- and surgery-associated factors, no statistically significant differences were found between the groups in gender, the cold ischemia time, the incidence of HLA mismatches, primary and/or repeated transplantation, positive bacteriology of PAP perfusate. The groups significantly differed in donor's age and causes of death. Thus, the prevalent cause of death was the acute cerebrovascular accident (CVA) in the Study group, and TBI in the Comparison group (Table 3).

Table 3. Characteristics of groups by donor- and surgery-associated factors

Number of transplantations	1st group (Study group) 51	2nd group (Comparison group) 10	P
Donor gender: male, % (n) female, % (n)	 62.7 (32) 37.3 (19)	 70 (7) 30 (3)	0.735
Donor age, years, Me (25-75%)	56 (52; 60)	47.5 (43; 49)	0.002
Cause of donor's death: Acute CVA, % (n) TBI, % (n)	 90.2 (46) 9.8 (5)	 60 (6) 40 (4)	0.032
Cold ischemia time, hours, Me (25-75%)	13.5 (10.5; 15)	11.25 (10; 13)	0.101
The number of HLA mismatches, Me (25-75%)	4 (3;5)	4.5 (4; 6)	0.227
First KT, % (n)	88.2 (45)	90 (9)	1.000
Repeated KT, % (n)	9.8 (5)	10 (1)	1.000
Third KT, % (n)	2 (1)	0	1.000
Positive cultures of kidney graft perfusate, % (n)	2 (1)	10 (1)	0.303

Immunosuppressive therapy. The baseline immunosuppression used in all patients included calcineurin inhibitors, mycophenolic acid preparations, and corticosteroids. Chimeric monoclonal anti-CD25 antibodies

(basiliximab) were used to prevent acute rejection in 45.1% of cases (n = 23) in the first group and in 50% of cases (n = 5) in the second group. Polyclonal antibodies, i.e. antithymocyte immunoglobulin (Atgam, thymoglobulin), were used with the same purpose in 23.5% (n = 12) and 20% (n = 2) patients if the 1st and 2nd group, respectively. In case of acute rejection, the treatment was initiated with the pulse therapy with methylprednisolone (3 injections, total 1-1.25 g); if no effect was seen, polyclonal antibodies and/or plasmapheresis sessions were administered.

The observation period and outcomes. A starting point of the observation period was KT, the final end-point was either the graft function recovery at in-hospital period, or the transplanted graft removal, or no prospects of a graft function recovery (based on the histologist report).

Investigations. In order to assess the renal graft condition and function, the following diagnostic tests were used: RAG ultrasonography and Doppler study, series of nephroscintigraphy studies over time. To verify the cause of delayed graft function (acute rejection, ischemia-reperfusion injury), a RAG biopsy was performed with a subsequent light microscopy and immunohistochemical examination. The computed tomography with oral contrast enhancement was performed in cases of graft dysfunction and/or the suspicion of developing vascular complications. Biochemical and clinical parameters of blood and urine were regularly assessed. The blood coagulation system parameters were regularly monitored; in case of hypercoagulation development, the indirect- and direct-acting anticoagulants were administered. Antiplatelet agents were used in all recipients for prophylactic purposes. From the first day, angioprotective and microcirculation-correcting drugs were prescribed in the group of KT recipients from suboptimal donors.

Statistical analysis of data was performed using the software package Statistica for Windows v.10.0, StatSoft Inc. (USA). The Shapiro-Wilk test was used to estimate the normality of the distribution. The Mann-Whitney test, the exact Fisher test, the χ^2 test for arbitrary tables were used for comparisons between the groups. The differences were considered statistically significant at $p<0.05$. For survival analysis, the standard life table method, the Kaplan-Meier survival tests were used. Survival curves were calculated from the date of surgical treatment. The mean length of hospital stay was 25 (21; 35), (min/max: 11/104) days.

Results

Among the total number of transplantations performed in the Sklifosovsky Research Institute for Emergency Medicine for the study period, the kidney transplants to elderly patients accounted for 11.9% (n = 16) in 2015; 17.3% (n = 30) in 2016; and 15.3% (n = 15) in the first 6 months of 2017. (Fig. 1).

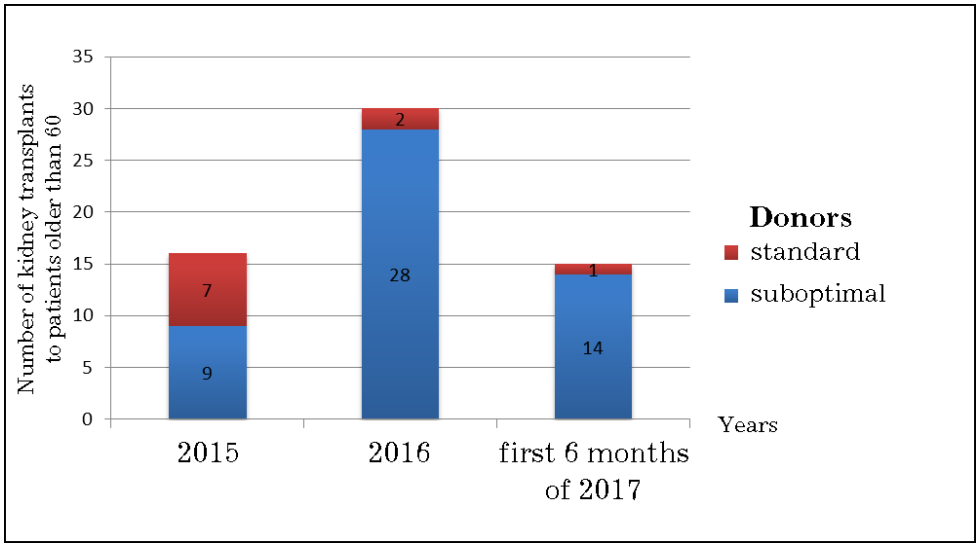


Fig. 1. Distribution of kidney transplantations performed in patients aged over 60 years with respect to donor type

Figure 1 demonstrated the increasing number of KTs in elderly patients, but the number of transplants from a standard donor performed in this category of patients dramatically decreased, while the number of transplants from suboptimal donors increased. Thus, the standard / suboptimal donor ratio changed from 43.7% / 56.3% to 6.7% / 93.3%.

A statistically significant relationship was found between the RAG initial function recovery and the donor organ quality. As it can be seen from Table 4, the delayed initial function and absent recovery of kidney graft function were statistically significantly more common in the group of kidney graft recipients from ECDs than in the kidney graft recipients from standard donors.

Table 4. Variants of the kidney graft function recovery in the investigated groups

Initial RAG function	1st group (Study group), n = 51	2nd group (Comparison group), n = 10	R
Immediate RAG function,% (n)	47 (24)	90 (9)	χ^2 (p = 0.043)
Delayed RAG function,% (n)	37.3 (19)	10 (1)	
PGNF *,% (n)	15.7 (8)	0	

* PGNF stands for primary graft non-function

The recipient survival differences with regard to the donor quality in the elderly recipients were not identified. The recipient survival rates in both groups were 100%. There were no recipient deaths.

A low early postoperative graft survival rate of 72.5% (n = 37) was seen in the group of RAG recipients from suboptimal donors. The graft survival rate in the Comparison group was 100% (Fig. 2).

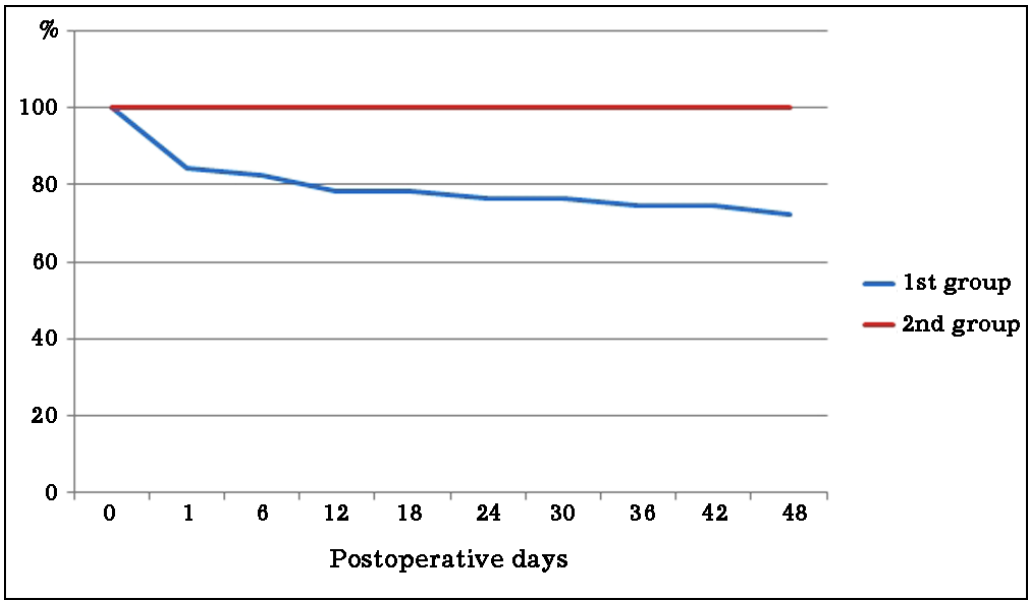


Fig. 2. Graft survival rates in early posttransplant period in elderly patients

The total graft loss in the early postoperative period accounted for 14 grafts (27.5%) in the patients of the 1st group, no cases of graft loss were documented in the 2nd group. The kidney graft function normalized in 30 patients of the Study group (58.8%) and in all the patients of the Comparison group; those differences were found statistically significant (Table 5).

Table 5. The final results of the transplanted kidney function at the time of patient transition to the outpatient treatment

	1st group (Study group), n = 51	**2nd group (Comparison group), n = 10**	**R**
Normalized RAG	58.8 (30)	100 (10)	

function, % (n)			0.044
Discharged with RAG dysfunction, % (n)	13.7 (7)	0	
Discharged for dialysis, % (n)	27.5 (14)	0	
Blood creatinine at the time of discharge*, μmol/L, Me (25-75%) (min, max)	148 (121; 170) 95-288	146 (121, 150) 106-156	0.384
Urea at the time of discharge*, mmol/L, Me (25-75%) (min, max)	11 (7.5, 14) 4.8-29	10.5 (7.8, 13) 5-13	0.483
GFR* ml/min, Me (25-75%) (min, max)	40 (36; 51) 16-85	47.5 (35; 52) 18-83	0.436
Length of hospital stay, days, Me (25-75%) (min, max)	25.5 (21.5, 37) ** 11-104	24 (21; 32) 17-62	0.621

* Patients with graft non-function were excluded from the group.
** Calculation for 48 patients in the 1st group.

The cause of the RAG loss in 11 cases was a donor-related factor (Fig. 3).

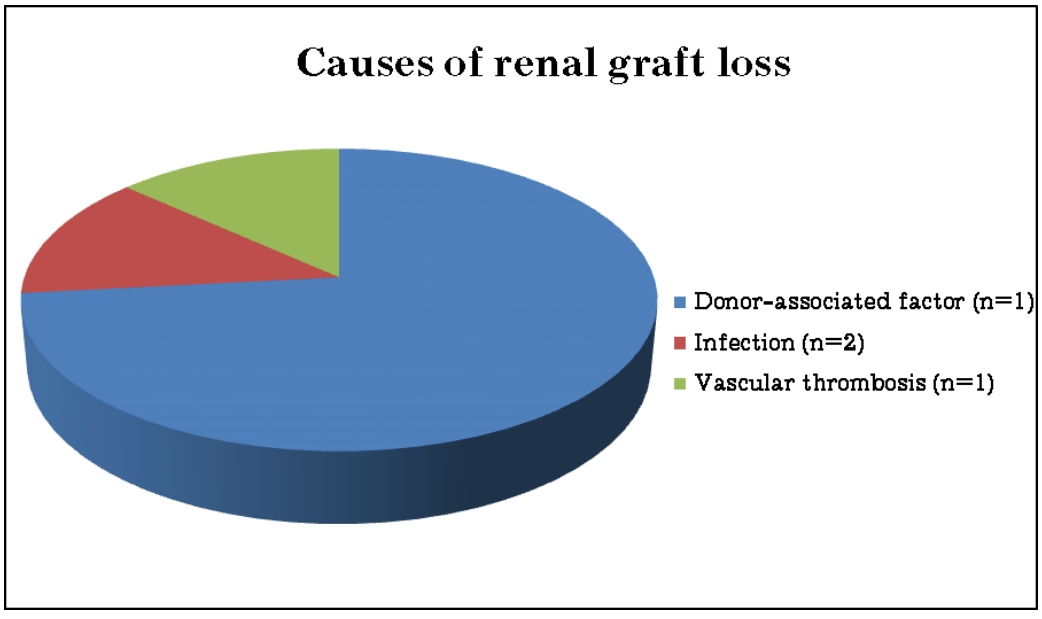


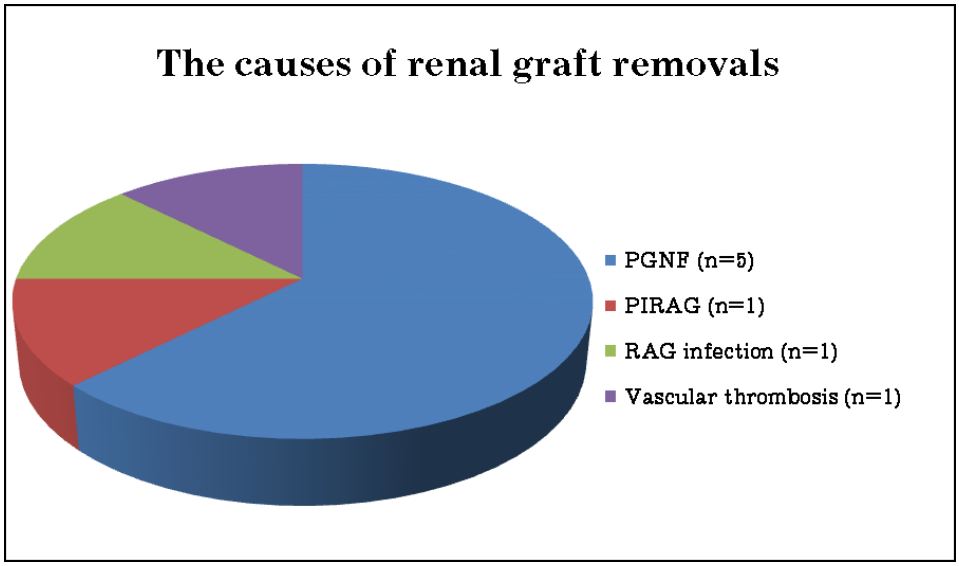
Fig. 3. The causes of the total renal graft losses in patients of the 1st group in the early postoperative period

Based on the biopsy results, the hypertensive nephroangiosclerosis, graft cortical necrosis, and thrombotic microangiopathy were diagnosed. There were 2 or 3 associated diagnoses in some cases. Of those, 8 cases were qualified as PGNF because there was no initial graft function; and despite the attempts to improve the graft condition with therapeutic measures (the anticoagulant administration, the attempts to elevate the blood pressure in recipients with severe hypotension, prescribing the drugs to improve microcirculation), the Doppler ultrasonography demonstrated an acutely depleted blood flow with progressive negative dynamics. In 3 cases, the inadequate RAG function recovery and the need to continue a renal replacement therapy with dialysis was caused by the initial severe dysfunction of the transplanted kidney; however, in those patients, only the water-elimination function recovered, no recovery of nitrogen excretory function was achieved.

Two more graft losses were associated with an infectious process. In one case, a RAG contaminated with *Klebsiella pneumonia* had been transplanted, which caused the arrosive bleeding from a. epigastrica inf. stump, an infectious lesion of a. iliaca externa walls; and that required an emergency renal graft removal and a cross femoral-femoral arterial bypass grafting. In another case, there was an ascending infection in the area of ureterocystoanastomosis, which required repeated inspections and also resulted in the graft removal.

In addition, in severe renal graft artery atherosclerosis in one case, the lower pole artery thrombosis developed with subsequent infarction of the RAG lower pole, which was also the indication for the graft removal.

In the group of kidney transplant recipients from ECDs, 8 transplantectomies were performed, which accounted for 15.7% of the transplanted kidneys in that group (Fig. 4).



* PIRAG stands for primarily infected renal allograft

Fig. 4. The causes of renal transplant removals in the early posttransplant period in the patients of the 1st group

The largest number of removed grafts included the PGNF cases with the morphologically confirmed development of cortical necrosis and necrotic alterations. There were no cases of renal graft removals in the group of RAG recipients from standard donors.

Discussion

The increase in the number of elderly posthumous donors has lately been seen in Russia, and it is also a worldwide trend. Thus, the CTS-collaboration reports a 6-26% increase in the proportion of kidneys transplanted from elderly donors to elderly recipients over a 25-year period [19]. According to the USA Registry, the number of transplanted kidneys

from ECDs in recent years has made 13.6-22.1% of the total number of donors [1, 18]. In the older age group, just over half of the recipients received organs from donors aged 50-64 years with unsatisfactory results in less than 4% of cases [19]. Most notably, a 5-year graft survival rate for RAGs from donors aged 50-64 years in elderly recipient group was only about 50% in the 1990s and it had increased to about 76.2% by 2005-2009 [19]. In our experience, the majority of RAG donors for the recipients in the elderly and older age groups have been suboptimal; and the RAG survival rate at 1.5-month after surgery is only 72.8%, which explains our study results and the differences from the world data.

Summary

Thus, the analyzed results of kidney transplantations from ECDs (suboptimal) to the recipients over 60 years in our hospital have been disappointing, since about 30% of renal allografts do not recover their function, which is associated with a poor quality of the donor organ due to the initial donor pathology unidentified at the donor management stage. We anticipate possible improvements of the kidney transplantation outcomes from making a mandatory preliminary biopsy of the grafts obtained from suboptimal donors to assess the nephrosclerosis severity and the suitability for transplantation. Also, it is necessary to take into account the anthropometric compliance of the organ donor and the recipient, the presence of systemic hemodynamic disorders in potential recipients, which requires that the final selection of the recipient should be made directly by specialists from the transplantation center, rather than by the MCCOD donor service, as is currently the case.

Conclusions

1. A significant increment has been recently observed in the number of renal transplantations from ECDs to elderly recipients, currently making 93.3% of the total number of kidneys transplanted to them.

2. A statistically significant deterioration of the initial RAG function and an increased PGNF incidence by 15.7% have been confirmed as related to organ transplantation from suboptimal donors.

3. No differences were found in recipient survival rates in the early postoperative period between the elderly recipient groups with respect to the donor organ quality: the recipient survival was 100% in both groups.

4. A statistically significant decrease in the graft survival in the early postoperative period has been found in the elderly recipients of RAG from ECDs: 72% vs. 100% RAG survival when obtained from the standard criteria donors.

5. A normalized RAG function was seen only in 58.8% of recipients in the Study group vs. 100% in the Comparison group.

6. The donor-associated factors have clearly been the most common causes of the RAG loss and the kidney transplant removals performed in the early postoperative period.

Conflict of interests. Authors declare no conflict of interests.

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