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COMPARATIVE ANALYSIS OF INDUCTION IMMUNOSUPPRESSIVE THERAPY PROTOCOLS IN RENAL TRANSPLANT RECIPIENTS (RETROSPECTIVE REVIEW)

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Objective: to evaluate the clinical efficacy and outcomes of kidney transplants performed using an alternative immunosuppressive therapy protocol that is based on double induction. **Materials and methods.** We examined 296 cases of kidney transplants performed in 295 patients between January 1, 2004 and December 31, 2018. Based on induction immunosuppressive therapy regimen, the patients were divided into two groups. Group 1 included patients who underwent transplantation from January 1, 2004 to June 30, 2013 and who used the standard induction immunosuppression protocol. Group 2 included patients who did transplant surgeries between the period January 7, 2013 and December 31, 2018 and who received the "double" induction protocol being analyzed. The method of dividing patients into these groups is associated with routine implementation of the analyzed protocol at the transplantation center since July 1, 2013. **Results.** Graft and recipient survival rates at all follow-up periods were higher in the group of patients who received the "double" induction immunosuppressive protocol than in the standard group. The studied protocol provides initially better and more stable graft function than in standard therapy. This is especially valuable in centers experiencing difficulties in assessing pre-transplant immunological risk. The graft and recipient survival rates achieved by the analyzed protocol are more pronounced in deceased-donor kidney transplantation. **Conclusion.** Positive results obtained from retrospective analysis of the protocol under study justify a prospective randomized study.

Keywords: kidney transplantation, recipient survival, immunosuppressive protocols, double induction immunosuppressive therapy.

IMPORTANCE OF THIS ISSUE

Kidney transplantation (KT) is currently the standard treatment for end-stage chronic kidney disease (ESCKD). It increases life expectancy, improves quality of life and provides social rehabilitation for kidney recipients [1]. Taking into account the economic efficiency of KT in comparison with other modalities of renal replacement therapy, its effective development at the state and regional levels stabilizes the entire health care system, enabling the most rational use of funding sources [2]. Despite improvements in immunosuppressive and adjuvant medication therapies and significant progress so far achieved in recent years in post-transplant survival rates, all recipients in the long-term period develop graft rejection to some extent, resulting in shortened duration of the graft function [3]. The initial state of the donor organ, the degree of immunological compatibility, the duration of cold, primary ischemia and secondary, warm ischemia, and the severity of reperfusion injuries equally play important roles in the long-term survival of kidney grafts and recipients [4]. Several of these factors lead to early graft dysfunction. Nonspecific lesions significantly increase the level of immune response, which requires increased doses of calcineurin inhibitors (CNIs), which have a nephrotoxic and additional damaging effect on the kidney graft, reducing its reparative capacity. Research has shown that delayed graft function is associated with a more pronounced incidence of acute rejection response [5]. Moreover, standard induction regimens are not always justified [6]. These factors make us look for new approaches to induction immunosuppressive therapy

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(IST) [7, 8] that would help to reduce additional damage, provide effective immunosuppression with delayed administration of calcineurin inhibitors, and reliable, long-term survival of patients and grafts [9].

Objective: to evaluate the clinical efficacy and outcomes of kidney transplants performed using an alternative double-induction immunosuppressive therapy.

The following tasks have been formulated to achieve this goal.

1. To compare kidney recipient and graft survival in the group that received the standard IST protocol and the group that received the double-induction IST protocol.
2. To assess kidney graft function in patients who received the standard IST and those who received the double-induction IST protocol.
3. To identify those patients that are expected to get better outcomes from double-induction IST regimen in comparison with the standard IST regimen.
4. To establish the structure of complications leading to adverse outcomes in kidney transplant recipients, depending on the IST regimen.

RESEARCH METHODOLOGY AND METHODS

The work was performed as a retrospective, open, nonrandomized, single-center, controlled study of the outcomes of kidney transplantations for a follow-up period covering January 1, 2002 to September 30, 2019. Clinical laboratory and instrumental research methods were used in the work.

MATERIALS AND METHODS

The study examined 296 kidney transplant surgeries performed in 295 patients from January 1, 2004 to December 31, 2018 at the kidney transplant department of the Republican Clinical Hospital, Kazan (Fig. 1). Based on the goal and objectives of the study, all patients were divided into two groups according to the IST regimen received. Group 1 included patients who underwent kidney transplant surgery within the period January 1, 2004 to June 30, 2013 and who used the standard IST protocol. Group 2 included patients who did transplant surgeries within the period January 7, 2013 and December 31, 2018 and who received the double-induction IST protocol. The method of dividing patients into these groups was associated with routine implementation of the protocol being analyzed at the transplantation center since July 1, 2013. Demographic indicators and structure of groups are presented in Table 1.

In group 1, immunosuppression therapy was administered according to the following protocol: pulse methylprednisolone therapy, basiliximab, calcineurin inhibitor with selection of dosage according to the drug concentration in blood, mycophenolic acid preparations. Accompanying therapy: proton-pump inhibitors, ganciclovir at a dose selected according to the glomerular filtration rate, then replaced with valganciclovir and co-trimoxazole. Perioperative antibiotic prophylaxis began 30 minutes before operation and lasted for 5–7 days (Table 2).

In group 2, immunosuppression was administered according to the following protocol: pulse methylprednisolone therapy, basiliximab, anti-thymocyte immunoglobulin. From day 4, the patients switched to basic immunosuppressive therapy, which included methylprednisolone, calcineurin inhibitor with dosage selection based on drug concentration in blood. Mycophenolic acid was administered from the day the lymphocyte count was

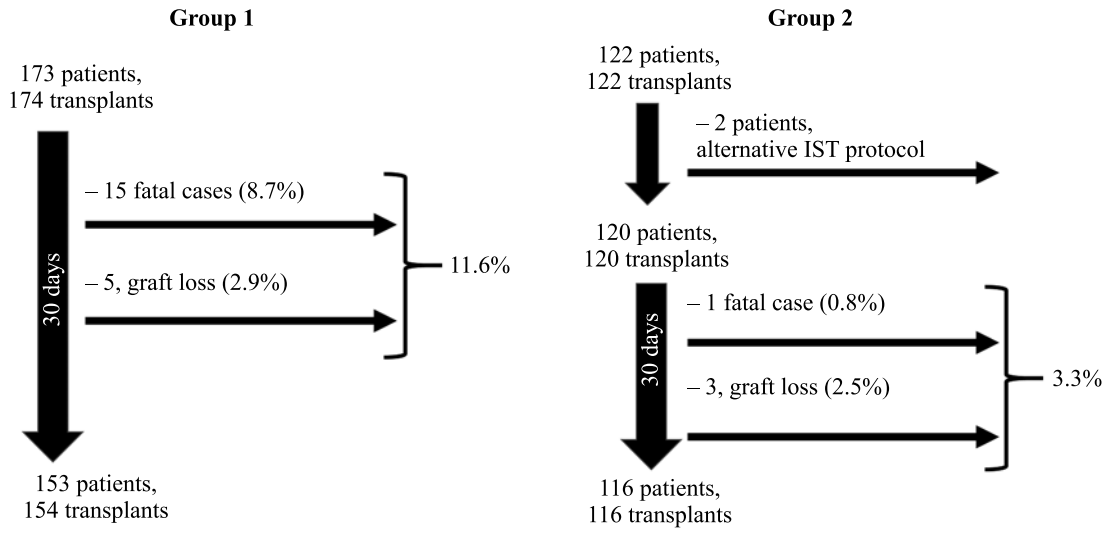

Fig. 1. Study design

Table 1

Demographic parameters and group structure

Parameters	Group 1	Group 2
Enrolled	01.01.04–30.06.13	01.07.13–31.12.18
Patients / Transplants, n	173 / 174	120 / 120
Age of recipients (years)	36 ± 1.0	34.5 ± 1.0
Age of recipients at KT from live donor (years)	28.1 ± 1.0	30.6 ± 0.9
Age of recipients at KT from cadaver donor (years)	43.1 ± 1.3	43.3 ± 1.7
KT from live donor / KT from cadaver donor	0.9 / 1	2.2 / 1
Male / Female	1.5 / 1	1.7 / 1
Diabetic nephropathy in TCKD structure (%)	9.8	8.3
Mismatch*	3.9 ± 1.0**	3.4 ± 1.0**

Note. * – antigens were determined only by A and B locus. Allocation of organs from deceased donors based on the less mismatches of A, B locus and negative Cross match results. ** – for the Mismatch analysis in cases of related kidney donation and coincidence of one antigen in A and B locus, one antigen in Dr locus was regarded as coinciding, in cases of deceased donation, antigens at the Dr locus always have been regarded as mismatching.

Table 2

Therapy protocol for patients of group No. 1

Days	–1	0	1	2	3	4	5	6	7	8	9	10	…
Methylprednisolone (mg)		500	500	500	250	250	250	24	24	24	24	24	↓
Basiliximab (mg)		20	–			20	–						
CNI inhibitor		±	+	+	+	+	+	+	+	+	+	+	↑↓
Mycophenolates			+	+	+	+	+	+	+	+	+	+	↑↓
Esomeprazole (mg)		40	40	40	40	40	–						
Omeprazole (mg)	–						20	20	20	20	20	20	+
Co-trimoxazole (mg)		480	480	480	480	480	480	480	480		480		6 months
Ganciclovir / valganciclovir (mg)		250	Under renal function control										200 days
Antibiotic therapy (amoxicillin / clavulanic acid)		+	+	+	+	+	+	?	?	–			
LMWH	±	+	+	+	+	+	+	+	+	+	+	+	–

Table 3

Therapy protocol for patients of group No. 2

Days	–1	0	1	2	3	4	5	6	7	8	9	10	…
Methylprednisolone (mg)		500	250	125	125	125	16	16	16	16	16	16	↓
Basiliximab (mg)		20	–			20	–						
Chloropyramine (mg)		20	20	20	20	–							
Paracetamol (mg)			500	500	500	–							
Anti-thymocyte immunoglobulin (mg)		50	50	50	50	–							
CNI inhibitor	–					Under blood concentration control							↑↓
Mycophenolates	–					Under leukocyte count control							↑↓
Esomeprazole (mg)		40	40	40	40	40	–						
Omeprazole (mg)		–					20	20	20	20	20	20	+
Co-trimoxazole (mg)		480	480	480	480	480	480	480	480	–	480	–	6 months
Ganciclovir / valganciclovir (mg)		250	Under renal function control										200 days
Antimycotics		+	+	+	+	–							
Antibacterial therapy (amoxicillin / clavulanic acid)		+	+	+	+	+	+	?	?	–			
LMWH	±	+	+	+	+	+	+	+	+	+	+	+	–

above 4×10^9/L. Accompanying therapy was similar and differed in the use of micafungin (Table 3).

Patients in both groups were monitored based on outcomes as of September 30, 2019. Patient deaths were analyzed, and kidney function indicators of recipients were studied for 12 months after transplantation.

RESULTS AND DISCUSSION

Due to the fact that to assess the efficacy and safety of the double-induction IST protocol, we used retrospective analysis method, and patients were divided according to IST protocol used on the basis of routine use of the study protocol since July 1, 2013. We excluded all cases of adverse outcomes that occurred in the first 30 days after surgery. The chosen approach allows minimizing the influence of such historically dependent factors as existing levels of anesthetic and intensive care support, and surgical technique. Results obtained (Fig. 1) show that adverse events associated with graft death or graft loss within a 30-day postoperative period was 11.6% in the group of patients who received the standard IST protocol, and 3.3% in the double-induction group. As a result, the number of subjects that continued the study in the first and second groups was 153 and 116 patients, respectively.

To assess the efficacy of immunosuppressive therapy protocols used for this general population, Kaplan–Meier curves for patient and graft survival were constructed (Fig. 2, 3).

The diagrams presented show that recipient survival and graft survival are higher in group 2 (double-induction IST protocol) by 4% and 10% respectively at year 3 of follow-up. The relative heterogeneity of the compared groups, which involves a different ratio of the number of transplants performed from a living relative and from a deceased donor, necessitated a separate analysis of the outcomes of recipient survival depending on the source of the donor organ (Fig. 4, 5).

When these data are compared over 6 years after operation, it can be seen that the differences in outcomes for living-donor transplant for up to 36 months are insignificant. Meanwhile, in deceased-donor kidney transplantation, at month 36 of follow-up, the double-induction IST protocol achieves a more than 10% patient survival and 20% graft survival. These data suggest that the more effective the double-induction IST protocol is, the more severely compromised the donor organ is and the higher the HLA incompatibility, which is typical for deceased organ donation.

In evaluating the effect of the protocol on kidney graft function, we analyzed the serum creatinine levels in kidney recipients who received an organ from a living donor in the period from 3 to 12 months (Fig. 6).

As can be seen from the data obtained, graft function, for a period of up to one year, was better with the double-induction protocol, showing lower average creatinine levels in recipients and a smaller degree of variation in this indicator. Similar results were obtained for recipients who received an organ from a deceased donor (Fig. 7).

Over the entire follow-up period, including in the first 30 days after transplantation, 51 patients died in the first group, and 8 in the second group. Cardiovascular disease was the main cause of death among patients who received the standard IST protocol (Fig. 8), whereas infectious complications was the main cause of death in the group that received the double-induction IST protocol (Fig. 9).

The prevalence of infectious complications in the double-induction group is probably due to a shorter follow-up period for these patients, with absolute values

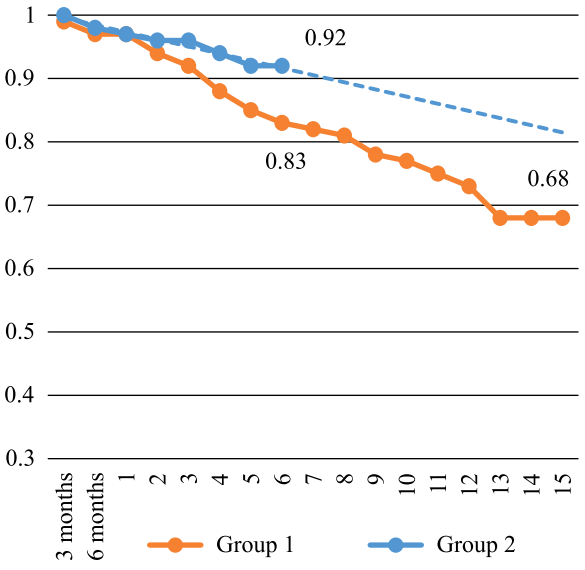

Fig. 2. Recipients survival

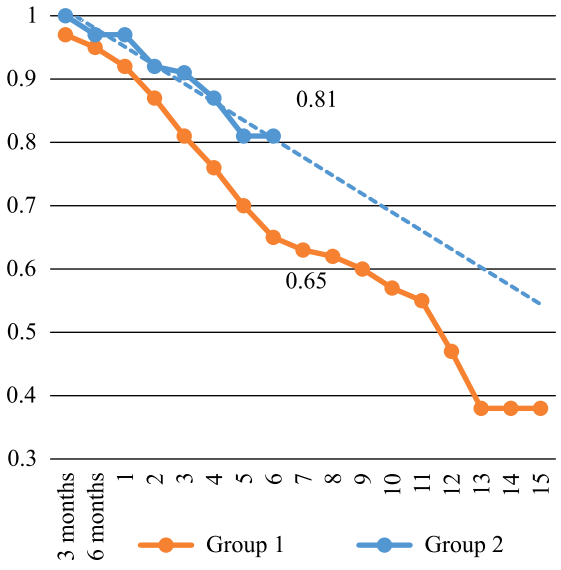

Fig. 3. Transplant survival

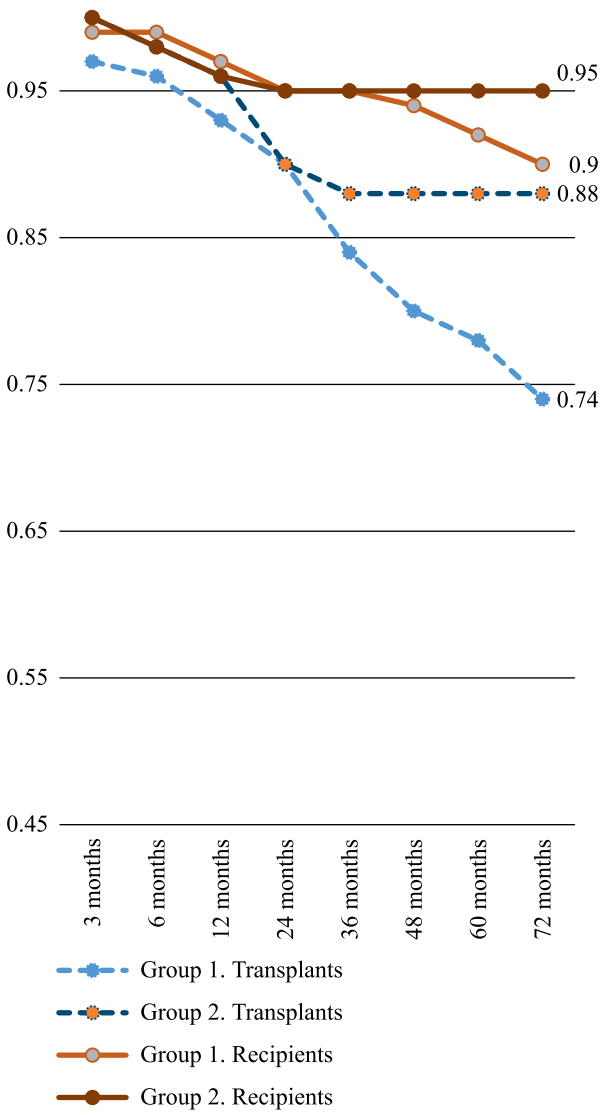

Fig. 4. Recipients and transplants survival after transplantation from alive donor

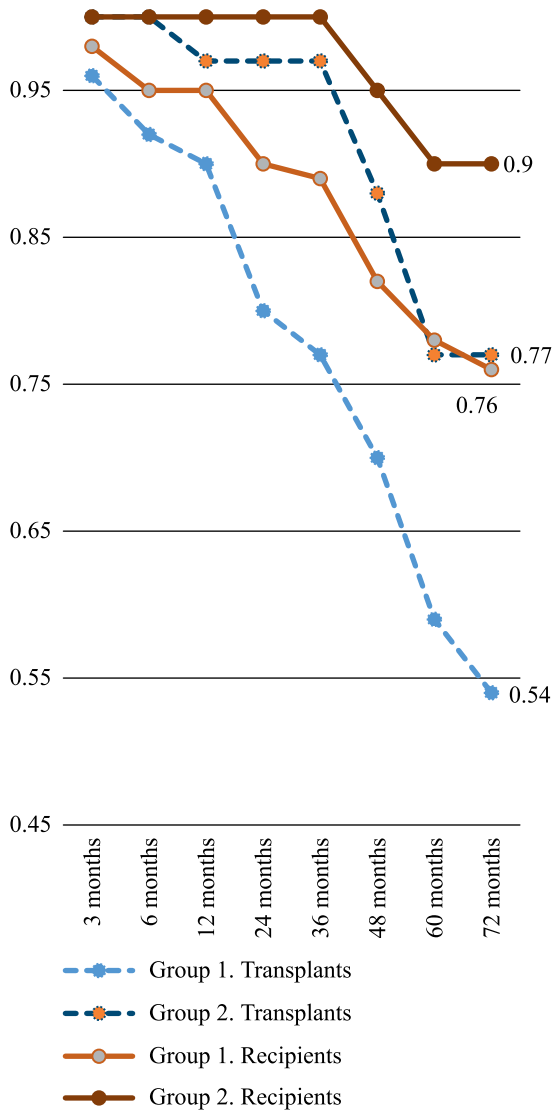

Fig. 5. Recipients and transplants survival after transplantation from deceased donor

of 15 cases in the standard IST group versus 5 in the study group.

Based on data obtained, it can be suggested that the observed results in the double-induction group were achieved due to the following factors: a) lower white blood cell count, leading to reduced severity of immunological response in the early postoperative period; b) pronounced induction immunosuppression makes it possible to delay CNI administration and maintain their lower concentration in the future, thereby reducing the negative nephrotoxic effect of CNIs in the kidney graft; c) against the background of depletion of lymphocytes most actively responding to donor antigens, basiliximab effectively inhibits interleukin-2 receptors in newly maturing and recruited CD4+ lymphocytes.

FINDINGS

1. Graft survival and recipient survival at all follow-up periods are higher in the double-induction IST group than in the standard IST group.
2. Double-induction IST protocol provides an initially better and stable kidney graft function compared to the standard IST protocol. This is especially valuable for centers experiencing difficulties in assessing pretransplant immunological risk (this makes it possible to prolong graft half-life to 5 years in group 2 compared to group 1).
3. The advantages of the double-induction protocol in recipient and graft survival is observed in deceased-donor kidney transplant to a greater extent.
4. In relative terms, infectious complications are the prevailing cause of mortality in kidney recipients who received the double-induction IST protocol. This is probably down to the shorter follow-up period for

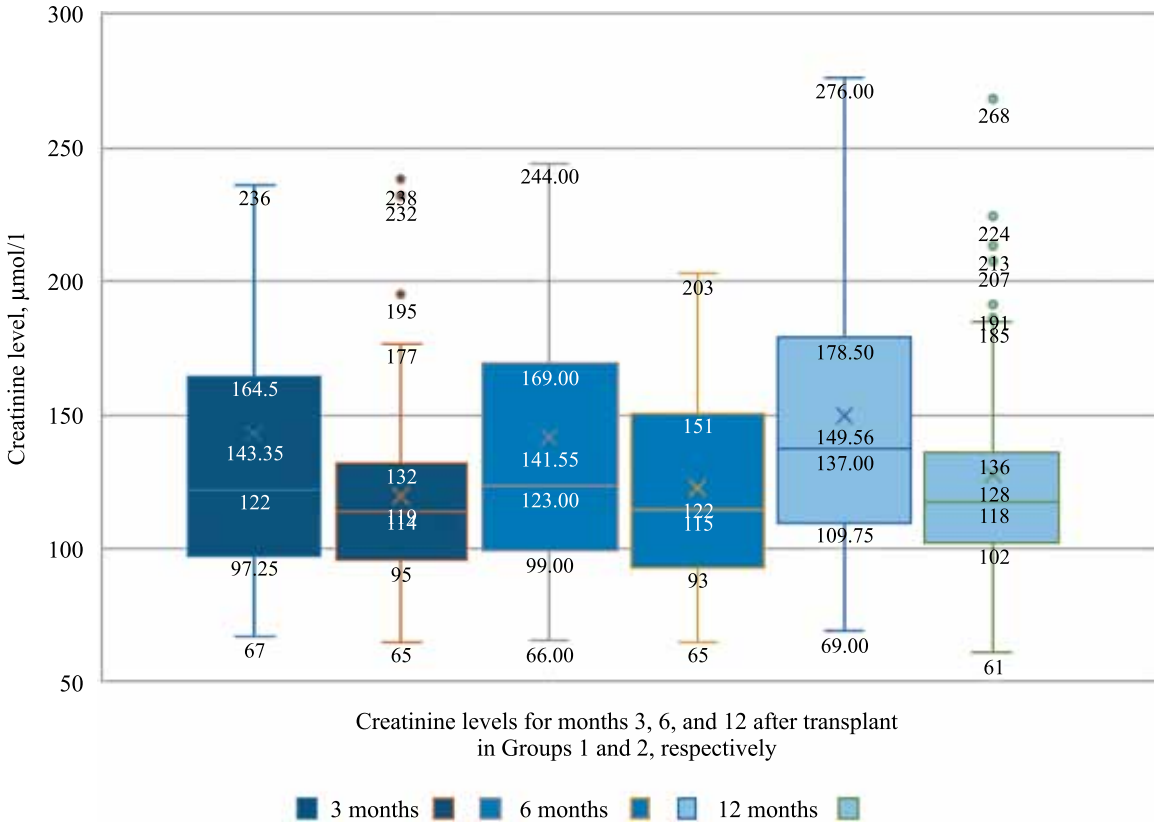

Fig. 6. Renal function in kidney recipients from alive donors

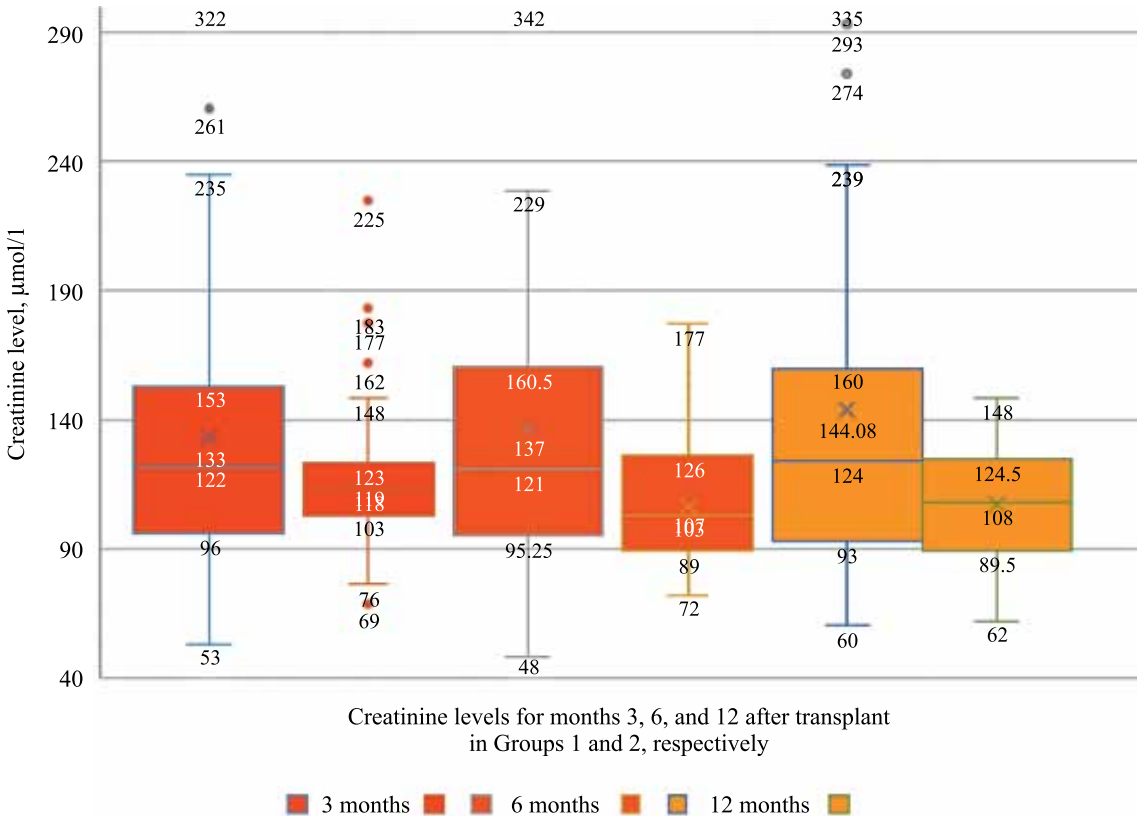

Fig. 7. Renal function in kidney recipients from deceased donors

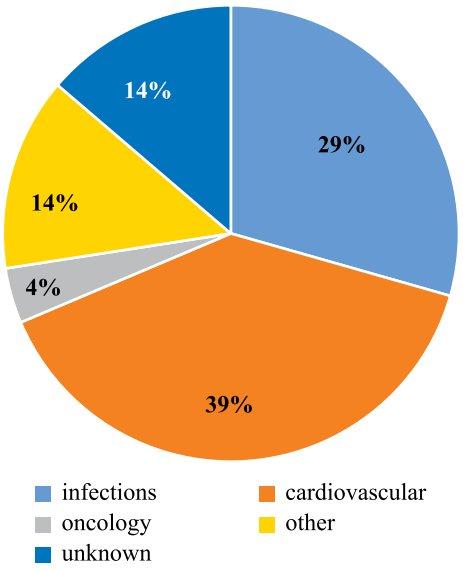

Fig. 8. The structure of mortality in group No. 1 (n = 51)

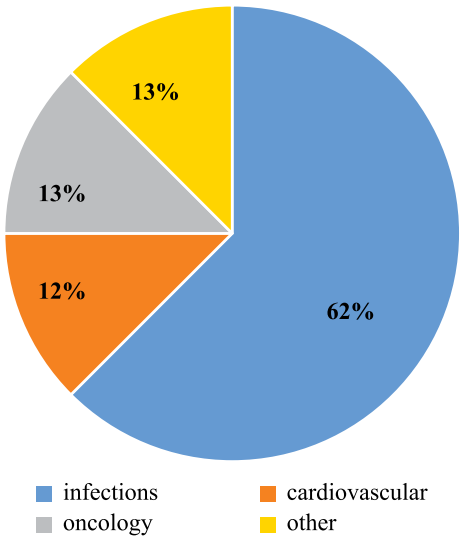

Fig. 9. The mortality structure in group No. 2 (n = 8)

this group, and possibly requires an assessment of whether or not baseline immunosuppression should be reduced.

The authors declare no conflict of interest.

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