



## Evolution of Renal Transplantation - 30-Year Experience from a Single Center

By Viktor Denisov, Vadym Zakharov, Eleonora Komissarenko, Eugene Onischenko, Tatyana Golubova, Sergey Kichatyi & Olga Zakharova

**Abstract- Aim:** To summarize our single – center experience in renal transplantation (RT), analyze the trends and review the influence of these trends on outcomes of RTx for further evaluation of its therapeutic potential and better understanding the tasks for professionals.

**Methods:** Our Center performed 705 kidney transplants (RTx) between April 1986 and October 2016. The median recipient age was 42.6 years with M:F ratio of 1.6:1. Most of them were on hemodialysis (96%), 28 patients received pre-emptive transplant, 517 (73.3%) transplants were from deceased donors, 184 (26.7%) were from living donors.

**Results:** Patients in the start and more late stage of transplant program had the following significant differences: the range of their age has been changed from 14-62 to 6-71 years. Transplantations from deceased donors decreased from 98.7% to 40.3% of cases.

**Keywords:** renal failure, organ donation, transplantation, immunosuppression, allograft dysfunction.

**GJMR-I Classification:** NLMC Code: WJ 368



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# Evolution of Renal Transplantation – 30-Year Experience from a Single Center

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**Methods:** Our Center performed 705 kidney transplants (RTx) between April 1986 and October 2016. The median recipient age was 42.6 years with M:F ratio of 1.6:1. Most of them were on hemodialysis (96%), 28 patients received pre-emptive transplant, 517 (73.3%) transplants were from deceased donors, 184 (26.7%) were from living donors.

**Results:** Patients in the start and more late stage of transplant program had the following significant differences: the range of their age has been changed from 14-62 to 6-71 years. Transplantations from deceased donors decreased from 98.7% to 40.3% of cases. Last decades, more and more patients who were not considered as transplant candidates earlier have been referred to kidney transplantation. Amount of high risk factors such as diabetes, systemic lupus erythematosus, amyloidosis and other increased dramatically. Miniinvasive and other modern surgery technology were introduced.

Immunosuppression at the beginning consisted of cyclosporine, azathioprine and steroids. Later in all cases of induction anti-CD-25 monoclonal or other depleting antibodies were used. Immunosuppression maintenance spectrum was added by tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium or everolimus. Over the last decade steroid-free protocols were used in about 30% of all primary RTx to avoid the long-term side effects of steroid use. Immunosuppression-free protocol in one recipient with normal graft function is using last 3 years.

Our data showed that in spite of extension of indications, the number of primary functioning kidney transplant increased from 71.2 % to 78.3 %. It makes the best start for long-term rehabilitation of recipients. One-year survival of high risk recipients was 95.7 % with a good quality of life. One-year graft and patient survival in standard conditions reaches 100%. The maximum term of satisfactory function of the kidney transplanted at our Center to 44-year-old patient with chronic glomerulonephritis, is more than 26 years. Monitoring continues. Long-term follow-up revealed a large and sometimes dominant influence of the social aspects on graft and patient's survival, as well as their quality of life.

**Conclusions:** The results of renal transplantation indicate the possibility of prolonged rehabilitation including high risk patients. The later improvement is related to expanding of

transplant activities through education and multidisciplinary strategies.

**Keywords:** renal failure, organ donation, transplantation, immunosuppression, allograft dysfunction.

**Core tip:** In this study we analyzed our single-center data of renal transplantation between 1986 and 2016 years. Last decades, more and more patients who were not considered as transplant candidates earlier have been referred to kidney transplantation. The results of renal transplantation indicate the possibility of prolonged rehabilitation including high risk patients. The later improvement is related to expanding of transplant activities through education and multidisciplinary strategies.

## I. INTRODUCTION

Donetsk Transplant Center performed 705 operations since the first renal transplantation on 17 April 1986 till October 2016. The study summarizes the experience of organizational, clinical, scientific and educational work of the Centre in order to identify further priorities for professionals.

## II. MATERIALS AND METHODS

Figure 1 provides the information of the annual number of kidney transplants at the Center. The data collected retrospectively. Renal failure was a consequence of chronic glomerulonephritis, pyelonephritis, hypertension, polycystic, hypoplasia and other abnormalities, kidney stones, diabetes, scleroderma, systemic lupus erythematosus, systemic vasculitis, renal cell cancer, amyloidosis, Gudpaschura syndrome, multiple myeloma diseases. The main disease was mostly glomerulonephritis - 78.2%. Polycystic disease, diabetes or other causes were more seldom (Figure 2). The median recipient age was 42.6 years with M:F ratio of 1.6:1. Most of them were on hemodialysis (96%), 28 patients received pre-emptive transplant, 517 (73.3%) transplants were from deceased donors, 184 (26.7%) were from living donors.

Maximal duration of dialysis treatment with anuria before surgery was 13 years. Recipients in early (until 2000) and later stages (since 2000) of our work had the age differences from 14-62 years to 6-71 years.

The rate of renal cadaveric donations during decades decreased from 99.7% to 41.6% cases. In the

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last decade more and more patients who weren't previously considered as a candidate for transplantation were included in the waiting list. Miniinvasive and other modern surgery technology were introduced. The 'Custodiol HTK Solution' was used for cold storage of kidney transplants. The cold ischemia time was usually no more than 24 hours. The maximum duration of cold ischemia time with primary graft function and successful outcome of renal transplantation was 47 hours.

List of used immunosuppressants include nearly all modern drugs. The maximum term of satisfactory function of the kidney transplanted at our Center to 44-year-old patient with chronic glomerulonephritis, is more than 26 years. Monitoring continues. In the article were analyzed different aspects of renal transplantation. To assess the obtained data we used methods of parametric statistics including definition of their accuracy according to Student's criterion.

### III. RESULTS

*The structure of the Transplant Center:* The search for the optimal structure of the Center cannot be considered as finished. Initially was created the department of chronic hemodialysis and kidney transplantation.

The type of organization in which "all doing everything," let to start the kidney transplant, but eventually exhausted itself. In 1998, this department was reorganized in the transplant Center. The Center include the transplantation department with the intensive care unit for 6 beds, organ recovery team, immunological and biochemical laboratories, dialysis department for 16 dialysis places and the consultative polyclinic reception.

The main tasks of the Center are a kidney transplantation from deceased or living related donors for adults and children's, and also preparing the conditions for a liver and pancreas transplantations. The Centre has modern equipment to do this. Organization which based on the multidisciplinary approach has established itself in the world as the most effective. Currently it's necessary the further improvement of the structure of transplant center as a base for the medical, scientific and educational work.

*Selection and preparation of candidates for renal transplantation:* Selection of candidates for kidney transplantation depends on the development of a network of dialysis units and transplant Center interaction with related specialists: nephrologists, internists, family physicians, pediatricians, endocrinologists. In our opinion, dialysis should be performed only under the absolute contraindications or the patient's informed refusal of kidney transplantation after consultation in the transplant Center. Kidney transplantation as the least expensive method must be

performed on the basis of the budget and have priority in relation to the funding of dialysis.

All candidates for transplantation pass the standard examination in order to exclude the absolute and relative contraindications for the surgery. We prepare the candidates with the bicarbonate hemodialysis on the modern equipment. In the treatment are used erythropoietin, calcitriol, antihypertensives and other drugs which are situationally appropriate.

*Organ donation:* The technical aspects of kidney donation generally resolved, although it continues to improve. We transplant the kidneys with multiple renal arteries, veins, doubled ureters and other expanded criteria. However, the shortage of organ is the main problem which affects transplant activity.

Picture 3 provides the information about types of donors for renal transplantation in the different years.

The trend of the recent years is increase the proportion of the living related donation, which is not able to solve the organ shortage problem. After introduction of legislation in 1999, "the presumption of informed consent" for the organ donation after death, renal transplantations from deceased donors decreased from 98.7% to 40.3% of cases. During the last decade the decision about donor supply begin by the examination the possibility of related donation. In the absence of conditions for its implementation the patient is included in the waiting list for cadaveric donation.

The current deficit is determined obsolete form of organization of organ donation which does not provide responsibility of staff in intensive care units for non-participation in the donor process. A retrospective analysis of mortality showed that up to 40% loss of donors account is the problem of identifying a potential donor. The reasons are in the insufficient training of the medical staff of intensive care units, lack of motivation, absents of equipment for the diagnosis of brain death and the fear that the activities associated with the donor process, will cause negative reaction of relatives, administration, law enforcement agencies, as well as complicate the implementation of normal usual work. The participation of staff of intensive care units in the implementation of the organ donation requires high skills and considerable additional efforts, a complex organizational and psychological challenge. It is necessary to strengthen the material-technical base of the intensive care units, to introduce the brain death diagnostic in the algorithms of management of patients with severe dominant brain damage. The intensification of work related to the donor procurement process must be payed adequately and this question should be decided by the state.

Important element of the work can be organization within the regional Center of emergency

medical mobile team of specialists for the diagnosis of brain death with the necessary equipment.

*Renal transplantation:* Operative technique of renal transplantation continues to improve, due to the expansion of indications and the desire to raise the profile of its safeness. Although kidney transplants still carried out in the iliac region as the world's first successful transplant in 1954 the number of technical complications and reoperation is significantly decreased, and changed their character. This is due to the appearance of selective immunosuppressants, improvement the quality of sutures, coagulation, surgical instruments, stents, lighting, the use of lenses. The possibility of organ recovery in heart-beating deceased donors or planned nephrectomy in living-related donors with modern storage solutions, anesthesia, respiratory devices and monitor observations excluded the development of complications associated with delayed graft function in renal. In our Center renal transplantation with simultaneous ipsilateral nephrectomy is an acceptable solution, when it is necessary to remove the patient's own kidneys or impossible to form uretero-vesical anastomosis. The possibility of early accurate identification and treatment of viral, fungal and bacterial infections is improved also.

All this has allowed us to increase the survival rate of transplant recipients. In the last years we have performed most RTx for the high risk candidates: children's (43), diabetics (27), patients with systemic diseases (11), third or fourth transplantation – (9), arenal conditions (7) and other risk factors (8). Despite the expansion of indications, the number of primary-functioning kidney transplant has increased from 71.2% to 78.3%. We agree with literature data that this provided a better starting point for long-term rehabilitation of the recipients [1-7]. The comparison of the significance of graft ischemia, rejection, thrombosis, infectious and drug-induced complications allows to consider ischemia the main reason of renal graft dysfunction. If anuria continued more than one month, than graft recovery usually was not observed. Only in one case patient diuresis was renewal and patient rehabilitated with creatinine level normalization on 45<sup>th</sup> day of anuria after renal transplantation. The largest volume of urine output immediately after renal transplantation to patient with lupus nephritis reached 51,3 liters per day. Ultrasound examination of the graft showed no pathology. The patients underwent an infusion of physiological polyionic solution in the "milliliter for milliliter" mode. On the 15th day after surgery, the patient was discharged from the department in good condition with normal graft function. One-year survival of patients in high-risk surgical group was 95.7% with a good quality of life, which corresponds to the modern level [8-10]. The one-year survival rate of transplant and patients in the standard conditions reached 100%. Figure 4 provide the

information about maximum graft survival in high risk RTx recipients.

*Immunosuppression:* Immunosuppression at the beginning consisted of cyclosporine, azathioprine and steroids. Later in all cases of induction anti-CD-25 monoclonal or other depleting antibodies were used. Immunosuppression maintenance spectrum was added by tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium or everolimus. Over the last decade steroid-free protocols were used in about 30% of all primary RTx to avoid the long-term side effects of steroid use (Table 1). Immunosuppression-free protocol in one recipient with normal graft function is using last 3 years.

Despite the low transplant activity, we register gradual increase of the number of observed recipients. During 2015 year we provide immunosuppressive monitoring for 139 recipients who lived in our region. Now immunosuppression after organ transplantation requires optimizing through regulation related to its organization, as well as training related professionals.

We have found that in the late postoperative period quality of life of recipients is largely determined by the presence or absence of anemia, hypertension, proteinuria, infection, renal transplant dysfunction. They demanded correction, effectiveness of which determinate the outcome of transplantation. It's consistent with the literature data [12-27].

A significant influence on the outcome of transplantation, especially in the long term period, provide non-compliance which is the basis on the loss of 25% of transplants.

In the context of immunosuppression after kidney transplantation late infections are developed more often than in the general population. They can be atypical, difficult and to be decisive in an unfavorable outcome.

Analysis of the structure of this infections showed that 70% were of viral origin, in 25.7% - bacterial, 4.3% - occurred tuberculosis. Symptomatic fungal infections in the late postoperative period were not observed.

The most difficult infections pass in the lungs and liver. In view of the data, to reduce the frequency and severity of late infection after kidney transplantation is necessary: vaccination against virus hepatitis B, the use of valganciclovir for prophylaxis and treatment of herpes viruses infections, prevention of communal infections among transplant recipients. The optimum is to provide the recipient a minimum but adequate immunosuppression within individual protocols on the basis of a wide range of modern selective immunosuppressants.

In general, the quality of life of patients with a satisfactory function of the renal transplant which is evaluated by using a questionnaire SF-36 (Short-Form

Health Survey), show that quality of life after RTx significantly higher than in dialysis patients, and approaches to the quality of healthy people life in all parameters (Table 2).

Progression of chronic renal allograft dysfunction is accompanied by the simultaneous loss of the benefits of a successful transplantation and the growth of problems due to immunosuppression. Based on a retrospective analysis of results of treatment of kidney transplant of the recipients with blood creatinine higher than 0.3 mmol/l, we adhere to the following principles in the correction of immunosuppression which allow to decrease the risk of complications in case of loss of its function.

1. Do not prescribe high doses of steroids and do not have the steroid pulse therapy.
2. Do not increase the dose of received cyclosporine or tacrolimus and stop medication if there is an increase of nephropathy.
3. To continue immunosuppression with mycophenolic acid which are not nephrotoxic.
4. To enhance monitoring of immunosuppression and prevention of infectious complications.
5. To cancel immunosuppression at returning to hemodialysis treatment. Cancellation of steroids should be done gradually - sometimes for several months. When the discomfort is associated with transplant (temperature, pain in the projection of the transplanted kidney, hematuria) short courses of low doses of steroids administered orally or intravenously can be effective.

*Educational, scientific, organizational and methodical work:* Today there is no doubt that the transplantology as a medical discipline should be including to the educational program for students and physicians of any profile. With our participation established programs, training manual, guidelines, tests, has accumulated a lot of information, including unique. As a result, the Centre introduced the teaching of transplantation for interns all medical specialties for 1 day and for interns' surgeons - 5 days. Allocated time does not permit to organize a full-fledged training.

This leads to late referral of the patients to the Center. It is difficult to help them because errors of the related professionals, the lack of an effective deceased donation, incorrect administrative decisions. Therefore, the work aimed at providing objective information to the public about organ transplantation is carried out by us on a permanent basis by all available means. However, to increase the effectiveness of this work is possible only with targeted state support.

Despite the fact that in the Center defended 2 doctoral and 12 candidate theses, the lack of clinical status reduces the attitude of medical personnel to transplantology as career discipline, reduces the

motivation for the research work, increases staff turnover.

#### IV. DISCUSSION

Almost everywhere in the world a significant intensification of transplant activity in a short time was provided at the governmental level in the framework of the standard and totally available technologies: adaptation of experts and the public opinion to perceive the concept of brain death as the criterion of human death, organization of transplant coordination, increase motivation in the implementation of the donor process [28]. Now, even in spite of the difficult conditions of wartime in Donbass past last years (since 2014), staff and material-technical base of Donetsk Transplant Center preserved and allow perform renal replacement therapy, including renal transplantation, to the way it was before the military conflict. In many ways, this contributed to a large unmet demand for this type of treatment and its good results, which is consonant with the positive international experience even in disaster medicine during renal replacement therapy [29].

Transplant surgery is based not only on technology but also on human solidarity and in fact reflects degree of maturity of a society. In the future, increasing the level of education and economic independence would create more trust and solidarity of social relations.

Transplantologists need to continue their work within the law, to promote the improvement of the regulatory framework and to get from the state correct perception of the problem of transplantology. The refusal to solve this problem creates social tension and poses a threat for the national security. Therefore, any measures aimed at improving transplant care are priority for the modern health care.

#### V. CONCLUSIONS

Our experience of renal transplantation confirms the principle possibility to achieve a guaranteed high level of patient's rehabilitation. The quality of medical and social rehabilitation after kidney transplantation is comparable with healthy individuals, and is much better than the patients being treated with hemodialysis.

It is necessary to increase the transplant activity. Important prerequisites to solve this problem fast enough are the global world progress and our own experience, if targeted state support will provide. State regulation in the field of kidney transplantation should be concentrated on the following priorities:

1. The decision of the legal and financial issues of strengthening the transplant center as a base for the development of clinical transplantation and optimal organizational form for the medical, scientific, educational and information work.

2. Optimization of the selection of candidates for a kidney transplant is providing mandatory centralized administrative check-up of all patients with renal insufficiency in renal transplant and total state budget funding of transplantation.
3. The introduction of diagnosis of death based on brain death in standards of intensive care units, an increase on the national level of motivation and commitment of staff of intensive care units participating in the donor process.
4. Ensuring public order to conduct information campaigns on organ transplants and the teaching of transplantation in the amount corresponding to the teaching of other clinical specialties, in order to create a positive public opinion about transplantation and increasing the professional level of specialists involved in the various stages of the transplantation.

*Supportive foundations:* We have analyzed only our own clinical experience outside of any special research projects. This manuscript was created on the author's initiative.

*Conflict-of-interest statement:* There is no conflict of interest to report.

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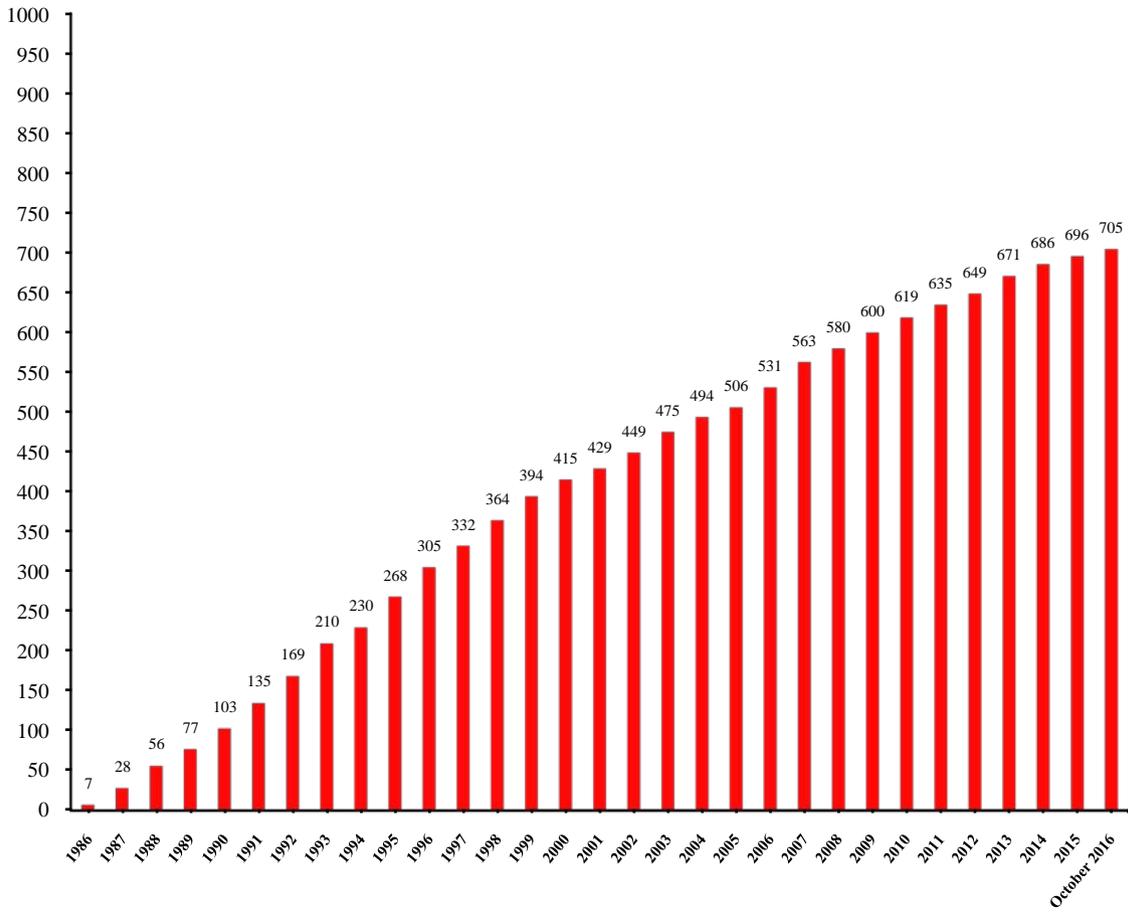


Figure 1: The cumulative number of renal transplants in Donetsk transplant center

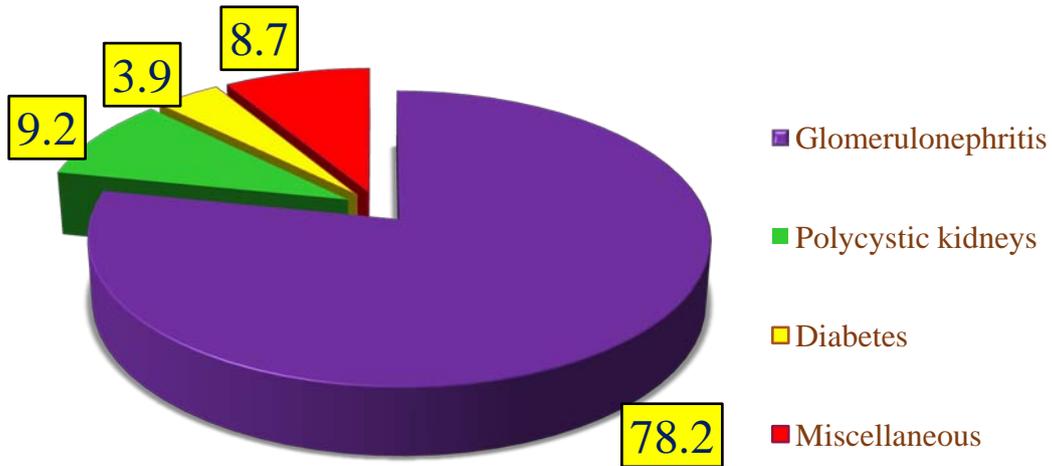


Figure 2: Etiology of end stage renal disease (%) in RTx recipients

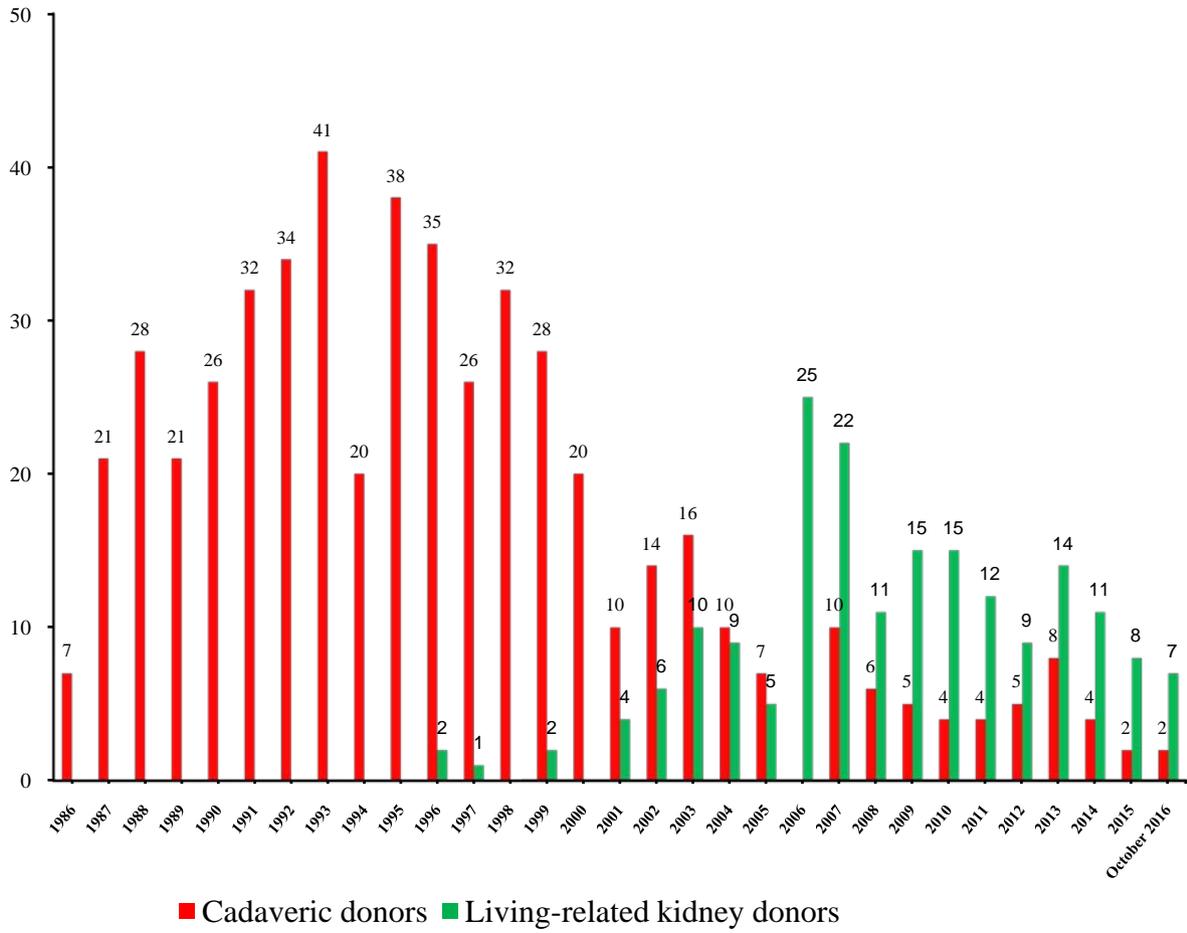


Figure 3: Types of donors for renal transplantation in the different years

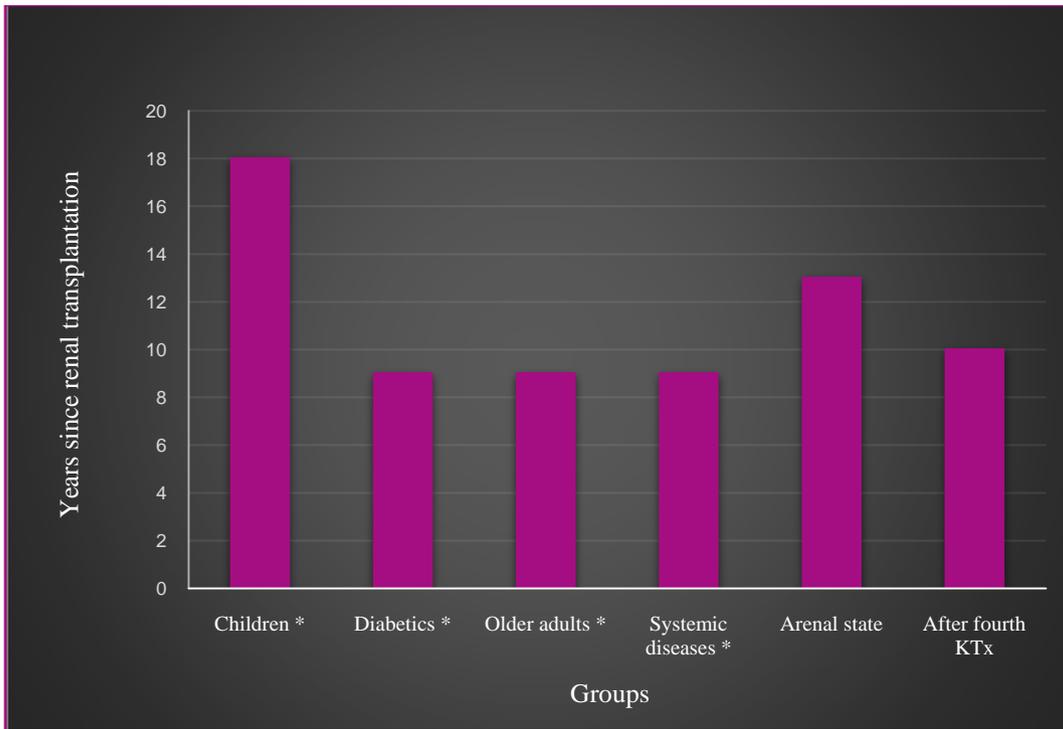


Figure 4: Maximum graft survival in high risk RTx recipients (\*monitoring continues)

Table 1: Current immunosuppression after renal transplantation in Donetsk transplant Center

Current immunosuppression
Anti-CD-25 monoclonal or other depleting antibodies – 100% (induction)
Cyclosporine – 75% (induction and maintenance)
Prolonged-release tacrolimus – 20% (induction and maintenance)
Tacrolimus – 3% (induction and maintenance)
Mycophenolate sodium – 63% (induction and maintenance)
Mycophenolate mofetil – 12% (induction and maintenance)
Azathioprine – 14% (maintenance)
Steroids – 100% (induction). Steroids – 70% (maintenance)
Everolimus – 5% (maintenance)

**Table 2:** Comparative description of life quality indices of patients treated with hemodialysis and the recipients with a satisfactory function of kidney transplant

Scales	Control (n=50)	Dialysis (n=62)	Transplants (n=63)
Physical Functioning	95,3±9,7	67,4±3,4	80,2±5,8*
Role-Physical Functioning	89,4±8,7	45,4±6,3	69,4±8,8*
Bodily pain	85,2±5,4	65,5±2,5	71,3±5,3*
General Health	73,2±6,2	43,5±4,7	60,5±6,1*
Vitality	59,7±4,9	49,1±4,5	56,2±4,6*
Social Functioning	85,0±8,8	29,0±3,2	45,3±5,7*
Role-Emotional	63,1±4,9	56,5±2,5	58,7±4,3*
Mental Health	62,8±4,5	59,5±3,5	60,7±5,4

Note. \* – differences between groups of dialysis and transplantation patients are statistically significant ( $P < 0,05$ ).