VOJNOSANITETSKI PREGLED
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ACCEPTED MANUSCRIPT

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Please cite this article **GRAFT AND PATIENT SURVIVAL AFTER RENAL TRANSPLANTATION IN THE PERIOD FROM 1996-2017 IN MILITARY MEDICAL ACADEMY, BELGRADE, SERBIA**

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UDC:

DOI: [https://doi.org/10.2298/VSP190313091V](https://doi.org/10.2298/VSP190313091V)

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
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Abstract

Introduction/Aim: Renal transplantation is the best and preferred way of treating patients with end-stage renal disease, as it offers improved survival and better quality of life in comparison to dialysis. The aim of this study is to show single-center results of the kidney allograft and patient survival during the period from 1996-2017. Methods: This is a retrospective, 22-year cohort study. Variables of interest were graft and patient survival in kidney transplanted patients. Age, gender, creatinine and induction therapy after transplantation were recorded in this group of patients as well. Results: Among 386 transplanted patients, 316 patients had a living donor and 70 patients deceased donor. Preemptive renal transplantation is done in 29 or 7.5% patients and ABO-incompatible kidney transplantation in 21 or 5.4% patients. One-year, 5-year, 10-year and 20-year overall patient survival after kidney transplantation in the observed group was 97.7%, 95.3%, 93.8% and 91.7%, respectively. One-year, 5-year, 10-year and 20-year graft survival in the our patients were 93.8%, 85.5%, 78.5% and 73.3%, respectively. Conclusion: The outcome of graft and patient survival in Military Medical Academy kidney transplantation program are good and in the line with the most eminent world centers.

Key words: kidney, transplantation; allograft; survival
Apstrakt

Uvod/Cilj: Transplantacija bubrega je najbolji i poželjan način lečenja pacijenata sa završnim stadijumom bubrežne bolesti, obzirom da nudi bolje preživljavanje i kvalitet života u poredenju sa dijalizom. Cilj ove studije je bio da prikaže rezultate jednog centra u preživljavanju pacijenata i allografta posle transplantacije bubrega tokom perioda od 1996-2017. godine. Metode: Ovo je retrospektivna dvadesetdvogodišnjakohortna studija. Parametri od interesa su bili preživljavanje allografta i pacijenata sa transplantiranim bubregom, a registrovani su i starost, pol, kreatinin i indukciona terapija nakon transplantacije. Rezultati: U posmatranoj grupi od 386 pacijenata sa transplantiranim bubregom, kod 316 pacijenata je urađena transplantacija od živog donora, dok je kod 70 pacijenata urađena transplantacija bubrega od kadaveričnog donora. Predijalizna transplantacija bubrega je urađena kod 29 ili 7,5% pacijenata, dok je transplantacija preko krvno-grupne barijere urađena kod 21 ili 5,4% pacijenta. Jednogodišnje, petogodišnje, desetogodišnje i dvadesetogodišnje preživljavanje pacijenata nakon transplantacije bubrega u ispitivanoj grupi je bilo 97,7%, 95,3%, 93,8% i 91,7%. Jednogodišnje, petogodišnje, desetogodišnje i dvadesetogodišnje preživljavanje grahta kod pacijenata sa transplantiranim bubregom je bilo 93,8%, 85,5%, 78,5% i 73,3%. Zaključak: Rezultati preživljavanja grahta i pacijenata u programu transplantacije bubrega u Vojnomedicinskoj akademiji su dobri i u skladu su sa rezultatima preživljavanja u najeminentnijim svetskim centrima.

Ključne reči: bubreg, transplantacija; allograft; preživljavanje
**Introduction**

Chronic kidney disease is an important health problem worldwide, since it is associated with increased risk of morbidity and mortality in this large group of population \(^1\). Renal transplantation is the best and preferred way of treating patients with end-stage renal disease, as it offers improved survival and better quality of life in comparison to dialysis \(^2,3\).

In most transplantation centers, one-year kidney graft survival in the transplant patients with living-donor and deceased-donor is between 90-98\% \(^4\). However, despite such good short-term results, the results of long-term graft survival are still unsatisfactory and have not been improved sufficiently over the last 20 years \(^5\). Data shows that hazard rates of graft failure at 10 years after transplantation is 64\%, and terminal graft dysfunction is, by frequency, one of the 5 most common reasons for starting a chronic dialysis program in countries in which a large number of kidney transplants have been performed in the past period \(^6,7\). This fact represents a major health, social and economic problem. Factors that affect the graft survival are numerous and can be divided into immunological and non-immunological \(^8\). Furthermore, results of graft and patient survival can also vary among individual regions due to the difference in certain patients and health care system characteristics, which may be important for the outcome of the transplantation.

The aim of this study is to show single-center results of the kidney allograft and patient survival during the period from 1996-2017.

**Material and Methods**

This is retrospective, 22-year cohort study during period from 1996 (when first kidney transplantation was performed in Military Medical Academy) till 2017. Study was performed in the Clinic of Nephrology and in the Center for Solid Organ Transplantation in Military Medical Academy, Belgrade. All patients who were transplanted and regularly controlled in our department were included in this study.

Variables of interest were graft and patient survival in kidney transplanted patients. Age, gender, creatinine and induction therapy after transplantation were recorded in this group of patients as well.
Although it changed over time, standard immunosuppressive protocol after kidney transplantation in our hospital included steroids (according to hospital practice); azathioprine until 1998, later replaced with micophenolat (mofetil and myfotis acid); and cyclospirine or tacrolimus (with C0 and C2 therapeutic monitoring for cyclosporine and C0 monitoring for tacrolimus). The mTor inhibitors were administered sporadically, initially as a replacement for calcineurin inhibitors (this practice was later stopped), in the cases of tumor formation after transplantation and, in recent years, in reduced doses with low doses of tacrolimus in some patients. During the last 10 years, patients were usually discarded from the hospital after kidney transplantation with steroids, micophenolat and tacrolimus. In patients who are considered to have a higher immunological risk, after cadaveric transplantation and in the cases of delayed graft function, induction therapy was applied in the form of Anti-Tymocite globulin or IL-2 antagonist.

Complete statistical analysis was done with the statistical software package, PASW Statistics 18. Attribute variables were presented as frequency of certain categories, while statistical significance of differences was tested with the Chi-square test. Numerical variables were presented as mean with standard deviation, while statistical significance of differences was tested with the Mann-Whitney test or Independent samples t test (normal or not normal distribution). All the analyses were estimated at p<0.05 level of statistical significance. Unadjusted graft and patient survival was calculated using Kaplan-Meier plots and p-values derived from the univariate Log-rank test.

Principles of ICH Good Clinical Practice were strictly followed and ethical approval No. 01/31-01-13 from the ethics committee of the hospital was obtained for the study protocol No. 910-1.

Results

During the observed period, total 445 kidney transplantations were done in Military Medical Academy. However, analysis in this study included 386 kidney transplant patients, since patients who were transplanted, but not regularly controlled in our hospital were not analysed (59 patients or 13.7%). Among 386 transplanted patients, 316 patients (81.9%) had a living donor and 70 patients (18.1%) deceased donor. Pre-emptive renal transplantation is done in 29 (7.5%), patients and ABO-incompatible kidney transplantation in 21 (5.4%)
patients, applying an original method for removal of ABO-isoagglutinins, which is explained elsewhere \(^9\)–\(^{11}\).

The 32.6% of all transplanted patients were females and 67.4% were males. Average age in all patients was 44.65 ± 10.46. Average age in male patients was 43.96 ± 10.12, and in female patients 45.35 ± 10.80 (Mann-Whitney test; \(p=0.604\)).

Induction therapy was performed in 98.5% transplantations in deceased-donor group and in 41.1% in living-donor group (Chi-square test; \(p<0.001\)).

One-year, 5-year, 10-year and 20-year overall patient survival after kidney transplantation in the observed group was 97.7%, 95.3%, 93.8% and 91.7%, respectively (Figure 1). Survival is better in the living-donor in comparison to the deceased-donor transplant recipients: 98.7%, 96.2% and 94.3% in the living donor, versus 92.9%, 91.4% and 91.4% in the deceased-donor group (Figure 2). However, 20-year overall patient survival in living-donor group was better for only 3.8% in comparing to deceased-donor group (Living-donor transplant recipients 92.4% vs. deceased-donor transplant recipients 88.6%; Log Rank test, \(p=0.090\)).

One-year, 5-year, 10-year and 20-year graft survival in the our patients were 93.8%, 85.5%, 78.5% and 73.3%, respectively (Figure 3). The 1-year, 5-year, 10-year and 20-year graft survival in the patients with living-donor renal transplantation were 93.3%, 84.8%, 76.6% and 70.6%, respectively, and 94.3%, 88.6%, 87.1% and 85.7% in the group of deceased-donor renal transplantation respectively, Log Rank test, \(p=0.295\) (Figure 4).

One-year, 5-year and 10-year patient survival in ABO incopatible kidney transplantat recipients were 100.0%, 90.5% and 90.5%, respectively (Figure 5). The 1-year, 5-year and 10-year graft survival in these patients were 80.9%, 76.2% and 71.4% (Figure 6).

In the group of pre-emptive kidney transplant recipients, 1-year, 5-year and 10-year patient survival were 100.0%, 100.0% and 96.5% (Figure 7), and the 1-year, 5-year and 10-year graft survival in these patients were 100.0%, 86.2% and 75.9%, respectively (Figure 8).

Average creatinine during the last follow-up examination in the living-donor group was 130.63 ± 63.73 µmol/L, while in deceased-donor group was 140.08 ± 60.22 (Independent samples t test; \(p=0.333\)).
Discussion

In our study, graft loss among living-donor and deceased-donor groups showed no significantly difference. In our study, one-year, 5-year, 10-year and 20-year overall patient survival after kidney transplantation in the observed group was 97.7%, 95.3%, 93.8% and 91.7%, respectively. On the other hand, one-year, 5-year, 10-year and 20-year graft survival in the our patients were 93.8%, 85.5%, 78.5% and 73.3%, respectively. In Europe, for deceased-donor renal transplant, overall 1-year graft survival was 90.6%, compared with three American populations: 91.5% for Hispanic Americans, 91.1% for white Americans, and 88.7% for African Americans. The 5-year graft survival was 77.0%, 72.9%, 71.3% and 62.5%, respectively, und the 10-year graft survival was 56.5%, 48.2%, 45.7% and 33.7%, respectively. For example, in Columbian study in the 164 patients with renal transplantation, patient survival at 5 years was 92.1%, but graft survival at 5 years was 88.4%. The 20-year patient survival rates were 37%, but graft survival rate was 13%. Wang et al. was shown that 5-year patient survival with deceased-donor in US, Australia and New Zealand, and Europe was 86.1%, 90%, and 87.1%, respectively. Five-year allograft survival with deceased-donor in US, Australia and New Zealand, and Europe was 72.4%, 81%, and 77.8%, respectively. On the other hand, 5-year patient survival with living-donor in US, Australia and New Zealand, and Europe was 93.1%, 95%, and 94.3%, respectively, while five-year allograft survival with living-donor in US, Australia and New Zealand, and Europe was 84.6%, 90%, and 86.9%, respectively.

Results of our study shows that the short and long term grafts and patient survival in our patients are comparable or even better in regard to results in the reputable centers worldwide. These results are particularly interesting because they include the beginnings of a kidney transplant program in our hospital. Important reasons for this are, doubtless, skilled surgical techniques, reliable tissue typing, careful patient care and frequent controls, as well as contemporary immunosuppressive therapy. However, certain demographic characteristics that may be somewhat specific and which may affect the results of transplantation should certainly be also mentioned. First of all, it can be concluded that patients in this study represent a rather typical sample of transplanted patients in our region: they are Caucasians (in our center was not African-American patients) and are relatively younger-age of patients at the time of transplantation were 44.5 years. Our
patients were younger compared to patients in some other areas, and correspond to the average age of transplanted patients in other centers in Serbia, as well as patients in our earlier study. There were more men in the group, which is also in line with our previous research, but also with the experiences of other authors. Epidemiological data shows that chronic renal failure and uremia occur more frequently in males. Comparison of men and women did not find a statistically significant difference in relation to age (p=0.604).

When analyzing our patients from the immune aspect, it can be concluded that their immunological risk were not high: the majority of transplants were made from a live donor. Kidney transplantation from a living donors certainly has its advantages—one of the most important is significantly shorter cold ischemia time and, consequently, lower incidence of delayed graft function and acute rejection which can result better long term graft survival. In some patients kidney transplantations were performed pre-emptive, which can be associated with the better graft survival. However, in our patients there was nevertheless a certain immunological risk: they were relatively young, and it is well known that these patients react immunologically stronger to the transplanted organ. Also, in the majority of patients in Serbia, the cause of terminal renal insufficiency was immunological (chronic glomerulonephritis). Also, it should be noted that the shortage of organs and a higher number of transplantations from a living donor results in the acceptance of the so-called "border" living donors, that is, older donors with a greater number of comorbid conditions. However, in relation to kidney transplanted patients in some other regions where African-American ethnicity patients are predominant and where a significant number of patients are retransplanted and/or sensitized, we can conclude that in our patients immunological risk still was moderate or lower. Less frequent application of induction therapy in living kidney transplantation program in our patients indirectly confirms this.

Globally more than 30% of patients awaiting renal transplant do not have an ABO-compatible donor in the family and, in circumstances when there is not enough kidney transplantation from a cadaver donor, realistic options for such patients are paired donor exchange and ABO-incompatible (ABOi) kidney transplantation. On the data from 2001 to 2010 in ABO-incompatible kidney transplantation group in Japan, patient and graft survival rates for the 1427 analyzed patients were an excellent 98 and 96% for the first
year, and 91 and 83% after 9 years, respectively. In our study, one- and 10 years patients with ABOi kidney transplant and allograft survival was 100.0% and 80.9%, and 90.5% and 71.4%, respectively. According to the conclusions from several transplant centers, this therapeutic option is acceptable for treating patients with end-stage renal disease, although it has been shown that these patients receive higher doses of immunosuppressive therapy, which puts them at increased risk not only of early, but also of delayed complications.

Pre-emptive kidney transplantation is considered the best available form of renal replacement therapy. This option is associated with improved patient and graft survival, better quality of life, and lower long-term medical costs compared with transplantation after dialysis initiation. In systematic literature review was shown that patient survival, graft survival and acute rejection rate were better in pre-emptive versus transplantation after start of dialysis. In Australian study, the 5-year survival in the pre-emptive kidney transplantation group was 97% and 10-year survival 93%, similar to our data. Therefore, pre-emptive transplantation should be the preferred modality of renal replacement therapy in patients who have a living donor.

Conclusion

The outcome of graft and patient survival in Military Medical Academy kidney transplantation program are good and in the line with the most eminent world centers. Further studies are needed which will more in detail clarify the influence of different factors on graft and patient survival in our patients.

Acknowledgment

The authors are in a position to present the basic and current results of the kidney transplant program at the Military Medical Academy. However, we owe special gratitude to our teachers, former heads of clinics of nephrology, center for kidney transplantation, vascular surgery, urology, immunology, radiology, neurology, anesthesiology, infectious diseases, cardiology, pulmology, endocrinology, microbiology, pharmacology, pharmacy as well as other branches and services without whose active participation and help such
complex and multidisciplinary field such as kidney transplantation would not be possible. Also, we feel the greatest gratitude to a great number of our colleagues, medical technicians and other medical staff who participated in the transplant program with great desire and dedication from the very beginning to the present. Their number exceeded the possibility of individual enumeration in this paper. All these people had a pioneering vision of the importance of kidney transplantation and have enabled these results with their commitment, faith, knowledge and care for each patient. The possibility of safe and routine performance of the kidney transplantations in our hospital presently stands on their shoulders.

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Figure 1. Overall survival in the patients with renal transplantation
Figure 2. Overall survival in the patients with renal transplantation according to living-donor or deceased-donor graft
Figure 3. Overall survival of graft in the patients with renal transplantation
Figure 4. Overall survival of graft in the patients with renal transplantation according to living-donor or deceased-donor graft
Figure 5. Overall survival in the patients with renal transplantation in blood group incompatible
Figure 6. Overall survival of graft in the patients with renal transplantation in blood group incompatible
Figure 7. Overall survival in the patients with pre-emptive renal transplantation

Survival Function

Cum Survival

Overall survival (years)
Figure 8. Overall survival of graft in the patients with pre-emptive renal transplantation

Received on March 13, 2019.
Revised on September 14, 2020.
Accepted September 28, 2020.
Online First September, 2020.