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Graft and patient survival after renal transplantation in the period from 1996 to 2017 at the Military Medical Academy, Belgrade, Serbia

Preživljavanje graftova i bolesnika sa transplantiranim bubregom u periodu od 1996. do 2017. godine na Vojnomedicinskoj akademiji, Beograd, Srbija

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Abstract

Background/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 compared to dialysis. The aim of this study was to present single-center (Military Medical Academy in Belgrade, Serbia) results of the kidney allograft and patient survival from 1996 to 2017. **Methods.** A retrospective 22-year cohort study was conducted. Variables of interest were graft and patient survival in kidney transplanted patients. Age, gender, serum creatinine levels, and induction therapy after transplantation were analyzed in this group of patients as well. **Results.** Among 386 transplanted patients, 316 had a living donor and 70 patients had a deceased donor. Pre-emptive renal transplantation was done in 29 (7.5%) patients and AB0-incompatible kidney transplantation in 21 (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 our patients were 93.8%, 85.5%, 78.5%, and 73.3%, respectively. **Conclusion.** The outcome of graft and patient survival in the Belgrade Military Medical Academy kidney transplantation program is good and in line with the leading world medical centers.

Key words:
age factors; creatinine; allografts; graft, survival; kidney transplantation; sex factor.

Apstrakt

Uvod/Cilj. Transplantacija bubrega je najbolji i poželjan način lečenja bolesnika sa završnim stadijumom bubrežne bolesti, s obzirom na to da omogućava bolje preživljavanje i kvalitet života u poređenju sa dijalizom. Cilj rada bio je da se prikažu rezultati jednog centra (Vojnomedicinska akademija u Beogradu, Srbija) u preživljavanju bolesnika i alografta posle transplantacije bubrega tokom perioda od 1996. do 2017. godine. **Metode.** Sprovedena je retrospektivna kohortna studija. Parametri od interesa bili su preživljavanje alografta i bolesnika sa transplantiranim bubregom, a analizirani su i starost, pol, nivoi kreatinina u serumu i indukciona terapija posle transplantacije. **Rezultati.** Od ukupno 386 bolesnika sa transplantiranim bubregom, kod 316 bolesnika je urađena transplantacija od živog donora, dok je kod 70 bolesnika urađena transplantacija bubrega od kadaveričnog donora. Predijalizna transplantacija bubrega je urađena kod 29 (7,5%) bolesnika, dok je transplantacija bubrega od donora sa nepodudarnom krvnom grupom urađena kod 21 (5,4%) bolesnika. Jednogodišnje, petogodišnje, desetogodišnje i dvadesetogodišnje preživljavanje bolesnika posle transplantacije bubrega u ispitivanoj grupi bilo je 97,7%, 95,3%, 93,8% i 91,7%, redom, dok je preživljavanje grafta u istim periodima iznosilo 93,8%, 85,5%, 78,5% i 73,3%, redom. **Zaključak.** Rezultati preživljavanja grafta i bolesnika u programu transplantacije bubrega na Vojnomedicinskoj akademiji su dobri i u skladu su sa onima u vodećim svetskim medicinskim centrima.

Ključne reči:
životno doba, faktor; kreatinin; alograft; graft, preživljavanje; transplantacija bubrega; pol, faktor.

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Introduction

Chronic kidney disease is an important health problem worldwide since it is associated with an increased risk of morbidity and mortality in this large population group [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 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 graft survival are numerous and can be divided into immunological and non-immunological ones [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 was to show single-center results of the kidney allograft and patient survival during the period from 1996 to 2017.

Methods

This retrospective, 22-year cohort study was conducted from 1996 (when first kidney transplantation was performed at the Military Medical Academy) till 2017. The study was performed at the Clinic for Nephrology and the Center for Solid Organ Transplantation at the Military Medical Academy, Belgrade, Serbia. All transplant patients who were regularly controlled in our Clinic were included in this study.

Variables of interest were graft and patient survival in kidney transplanted patients. Age, gender, serum creatinine levels, 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 mycophenolate (mofetil and myfortic acid), and cyclosporine 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. For removal of AB0 isoagglutinins from the blood in AB0-incompatible kidney allograft recipients, an original method was performed [9–11]. During the last 10 years, patients were usually discarded from the hospital after kidney transplantation with steroids, mycophenolate, 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 interleukin (IL)-2 antagonist.

Complete statistical analysis was done with the statistical software package PASW Statistics 18. Attribute variables were presented as the frequency of certain categories, while the statistical significance of differences was tested with the χ^2 test. Numerical variables were presented as mean with standard deviation, while the 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 a $p < 0.05$ level of statistical significance. Unadjusted graft and patient survivals were calculated using Kaplan-Meier plots and *p*-values derived from the univariate Log-rank test.

Principles of the International Conference of Harmonization (ICH) Good Clinical Practice were strictly followed, and Ethical approval No. 01/31-01-13 from the Ethics Committee of the Military Medical Academy in Belgrade was obtained for the study protocol No. 910-1.

Results

During the observed period, a total of 445 kidney transplantations were done at the Military Medical Academy in Belgrade. However, analysis in this study included 386 kidney transplant patients since patients who were transplanted but not regularly controlled in our hospital were not analyzed [59 (13.7%) patients]. Among 386 transplanted patients, 316 (81.9%) patients had a living donor and 70 (18.1%) patients had a deceased donor. Preemptive renal transplantation was done in 29 (7.5%) patients and AB0-incompatible kidney transplantation in 21 (5.4%) patients.

Out of all transplanted patients, 32.6% were females and 67.4% were males. The average age in all patients was 44.65 ± 10.46. The 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 (χ^2 test; $p < 0.001$).

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

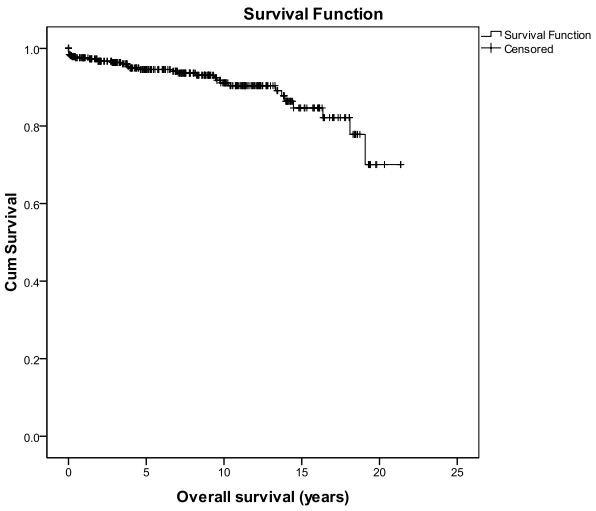


Fig. 1 – Overall survival of the patients with renal transplantation.

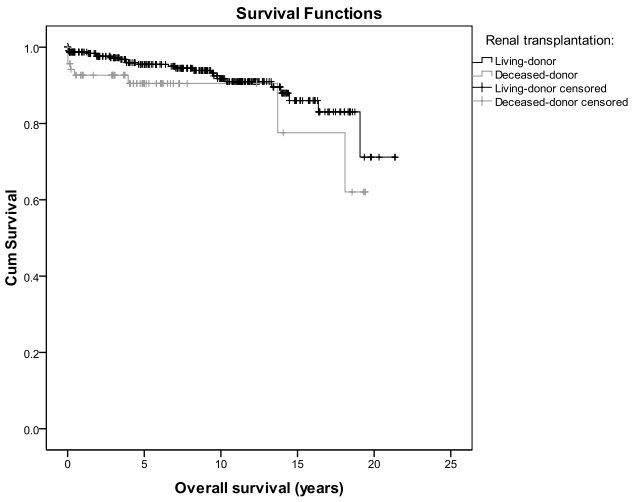


Fig. 2 – Overall survival of the patients with renal transplantation according to living-donor or deceased-donor graft.

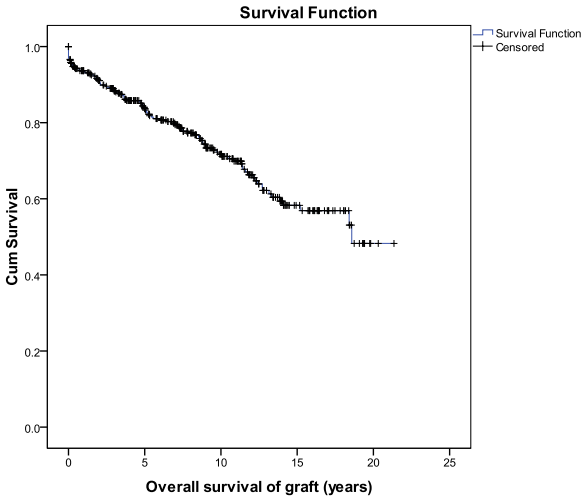


Fig. 3 – Overall survival of graft in the patients with renal transplantation.

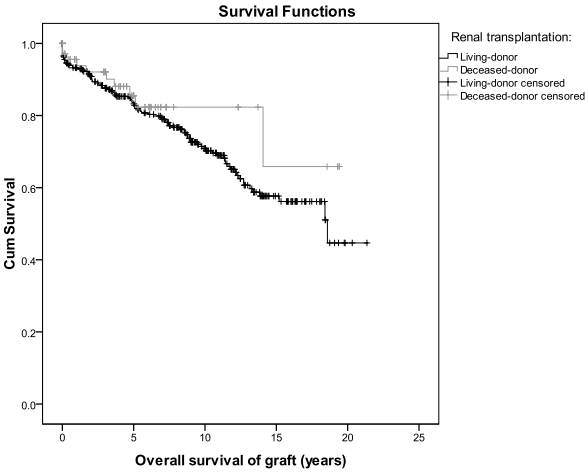


Fig. 4 – Overall survival of graft in the patients with renal transplantation according to living-donor or deceased-donor graft.

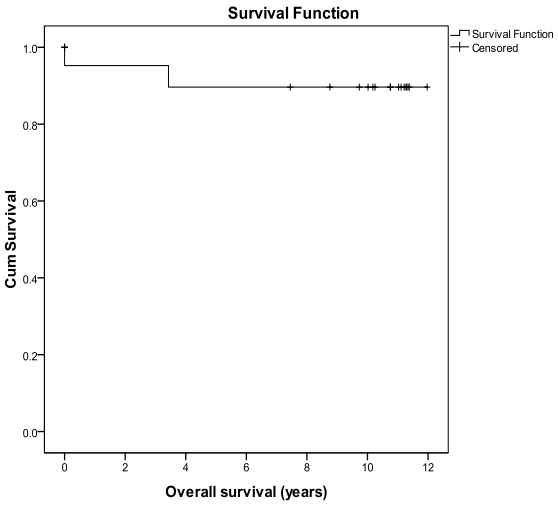


Fig. 5 – Overall survival of the patients with renal transplantation who did not an AB0–compatible donor.

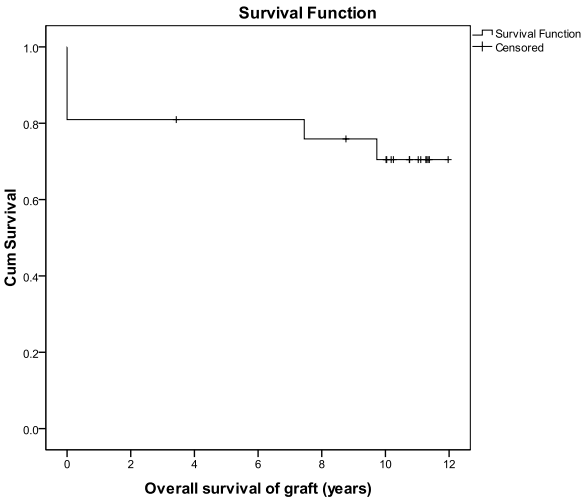


Fig. 6 – Overall survival of graft in the patients with renal transplantation who did not an AB0–compatible donor.

The 1-year, 5-year, 10-year, and 20-year graft survival in 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).

The 1-year, 5-year, and 10-year patient survival in AB0-incompatible kidney transplant 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%, respectively (Figure 6).

In the group of preemptive kidney transplant recipients, 1-year, 5-year, and 10-year patient survivals were 100.0%, 100.0%, and 96.5%, respectively (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 serum creatinine level during the last follow-up examination in the living-donor group was 130.63 ± 63.73 μmol/L, while in the deceased-donor group was 140.08 ± 60.22 (Independent samples *t*-test; $p = 0.333$).

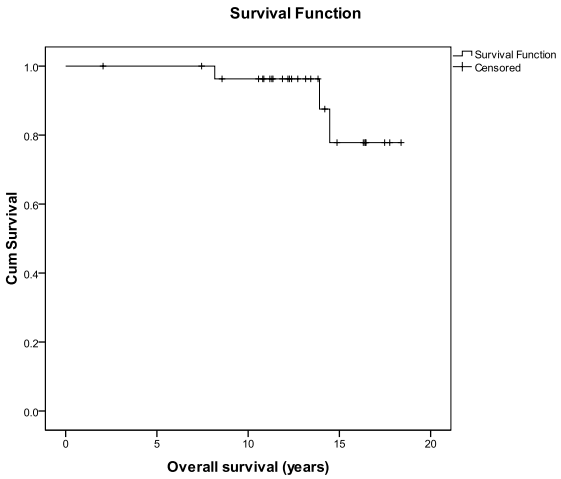


Fig. 7 – Overall survival of the patients with pre-emptive renal transplantation.

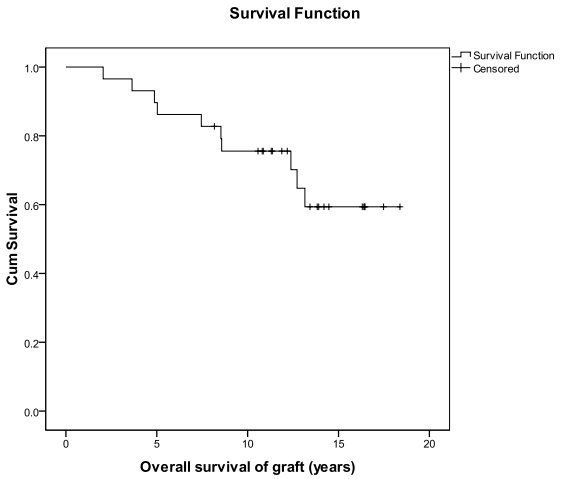


Fig. 8 – Overall survival of graft in the patients with pre-emptive renal transplantation.

Discussion

In our study, graft loss among living-donor and deceased-donor groups showed no significant difference. In our study, the 1-year, 5-year, 10-year, and 20-year overall patient survival after kidney transplantation in the observed group were 97.7%, 95.3%, 93.8%, and 91.7%, respectively. On the other hand, the 1-year, 5-year, 10-year, and 20-year graft survival in 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 [12]. The 5-year graft survival was 77.0%, 72.9%, 71.3%, and 62.5%, respectively, and the 10-year graft survival was 56.5%, 48.2%, 45.7%, and 33.7%, respectively [12]. For example, in a Columbian study, in 164 patients with renal transplantation, patient survival at 5 years was 92.1%, but graft survival at 5 years was 88.4% [1]. The 20-year patient survival rate was 37%, but graft survival rate was 13% [13]. Wang et al. [4] showed that 5-year patient survivals with deceased-donor in the US, Australia and New Zealand, and Europe was 86.1%, 90%, and 87.1%, respectively [4]. Five-year allograft survival with deceased-donor in the US, Australia and New Zealand, and Europe was 72.4%, 81%, and 77.8%, respectively [4]. On the other hand, 5-year patient survival with living-donor in the US, Australia and New Zealand, and Europe was 93.1%, 95%, and 94.3%, respectively, while five-year allograft survival with living-donor in the US, Australia and New Zealand, and Europe was 84.6%, 90%, and 86.9%, respectively [4].

Results of our study showed that the short and long-term grafts and patient survivals in our patients were comparable or even better in regard to the results in reputable centers worldwide. These results are particularly interesting because they include the beginnings of the kidney transplant program in our hospital [14]. Important reasons for this are doubtless, skilled surgical techniques, reliable tissue typing, careful patient care, frequent controls, and contemporary immunosuppressive therapy [15, 16]. However, certain demographic characteristics that may be somewhat specific and which may affect the results of transplantation should certainly be mentioned as well. 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, there were no African-American patients) and are mostly of younger-age (patients at the time of transplantation were 44.5 years in average). Our patients were younger compared to patients in some other areas [17] and the average age of transplanted patients corresponded to those patients in other centers in Serbia [18], as well as patients in our earlier study [19]. There were more men in our group, which is also in line with our previous research [19] but also with the experiences of other authors [4–6, 17, 18]. Epidemiological data shows

that chronic renal failure and uremia occur more frequently in males [8, 20]. No statistically significant difference concerning age was found in comparing men and women (p = 0.604).

When analyzing our patients from the immune aspect, it can be concluded that their immunological risks were not high: the majority of transplants were made from live donors. Kidney transplantation from 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 in better long-term graft survival [21]. In some patients, kidney transplantations were performed preemptively, which can be associated with better graft survival [21–23]. 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 [24]. Furthermore, in the majority of patients in Serbia, the cause of terminal renal insufficiency was immunological (chronic glomerulonephritis) [25]. Moreover, it should be noted that the shortage of organs and a higher number of transplantations from living donors results in the acceptance of the so-called "border" living donors, *ie*, older donors with a greater number of comorbid conditions [26]. 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 [27], we can conclude that in our patients, immunological risk was still moderate or lower. Less frequent application of induction therapy in living kidney transplantation programs in our patients indirectly confirms this.

Globally, more than 30% of patients awaiting renal transplant do not have an AB0-compatible donor in the family and, in circumstances when there is not enough kidney transplantation from a cadaveric donor, realistic options for such patients are paired donor exchange and AB0-incompatible (AB0i) kidney transplantation [28]. In the data from 2001 to 2010 in the AB0i kidney transplantation group in Japan, patient and graft survival rates for the 1,427 analyzed patients were an excellent 98% and 96%, respectively, for the first year, and 91% and 83% after 9 years, respectively [29]. In our study, the 1-year and 10-year survival of patients with AB0i kidney transplant and allograft survival were 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 [30], 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 [29].

Preemptive kidney transplantation is considered the best available form of renal replacement therapy [31]. This option is associated with improved patient and graft survival, a better quality of life, and lower long-term medical costs compared with transplantation after dialysis initiation. In a systematic literature review, it was shown that patient survival, graft survival, and acute rejection rate were better in preemptive versus transplantation after the start of dialysis [31]. In an Australian study [32], the 5-year survival in the preemptive kidney transplantation group was 97% and 10-year survival was 93%, similar to our data. Therefore, preemptive transplantation should be the preferred modality of renal replacement therapy in patients who have a living donor [32].

Conclusion

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

Acknowledgment

We owe special gratitude to our teachers, former heads of clinics (for nephrology, vascular surgery, urology, neurology, anesthesiology, infectious diseases, pulmonology, endocrinology), centres (for clinical pharmacology), institutes (of radiology, medical research, microbiology), Pharmacy Department as well as other branches and services in the Military Medical Academy in Belgrade without whose active participation and help such complex and multidisciplinary field as kidney transplantation would not be possible. In addition, 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. All of them 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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