Outpatient Period After Kidney Transplantation – Frequency of Complications and Their Impact on Graft and Patient Survival

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Abstract. *Background and objective: The growing numbers of kidney transplantations in recent years mainly focus our attention on the possibilities to prolong kidney graft and recipient survival, searching for methods to minimize post-transplant complications, which may have an adverse effect on outcomes of kidney transplantation. Despite innovations in the field of immunology and modern diagnostic and therapeutic novelties in recent years, the main challenge remains the improvement of a long-term kidney transplant and recipient survival. The outpatient period is very important to long-term kidney transplant survival. The aim of our study was to analyze outpatient period complications after kidney transplantation and identify factors during the outpatient period influencing kidney transplant and recipient survival.*

Materials and methods: We analyzed the rate of outpatient period complications, their dependence on the time after transplantation and influence of these complications on the graft and recipient survival in 249 renal transplant patients.

Results: The causes of recipient death during the whole outpatient period were infection 31.8% (n = 7), cardiovascular events 31.8% (n = 7), sudden death 18.2% (n = 4), other 9.1% (n = 2) and unknown reasons 9.1% (n= 2). The reasons of graft loss during the whole outpatient period were chronic allograft nephropathy/glomerular diseases 42.8% (n = 13), infection 37.0% (n = 10), acute rejection 7.4% (n = 2) and other 7.4% (n = 2). Infectious complications were the most common complications of the outpatient period. Urinary tract infection was diagnosed in more than a half of our patients (57.5%) and more often during the first year after kidney transplantation (44.1%). Sepsis was diagnosed in 48 recipients (19.3%). Sepsis (log-rank P = 0.012), urinary tract infections (log-rank P = 0.024), acute rejection (log-rank P = 0.032) and pneumonia (log-rank P = 0.024) which occurred during the outpatient period were significantly associated with worse overall graft survival. The occurrence of sepsis during the whole outpatient period and during the first year after transplantation was significantly associated with worse recipient survival (log-rank P = 0.014 and log-rank P = 0.004, respectively).

Conclusions: Infectious complications were the most common complications of the outpatient period. Urinary tract infections were diagnosed in more than a half of our patients after kidney transplantation. During the first year after transplantation, sepsis was diagnosed in 11.6% of the recipients and the main gate of infection was urinary tract. Acute rejection was diagnosed in 12% of our recipients during the outpatient period. Outpatient post-transplant period complications, such as sepsis, acute rejection, pneumonia and urinary tract infections (first year after transplantation), were significantly negatively associated with graft survival. Recipient survival was negatively associated with sepsis. The main reasons for graft loss in our recipients were infectious complications, chronic allograft nephropathy, and glomerular diseases. The main reasons for mortality after kidney transplantation were infectious complications and cardiovascular events.

Introduction

The growing number of patients with chronic kidney disease and end-stage kidney failure leads to the rising interest of care, treatment, and outcomes of these patients. Kidney transplantation is a choice method of renal replacement therapy. The number of kidney transplantations in Lithuania has increased by 60% since 2005 [1, 2] and in 2013 reached 28 p.m.p. [2]. The growing numbers of kidney transplantations in recent years mainly focus our attention on the possibilities to prolong kidney graft and recipient survival, searching for methods to minimize post-transplant complications, which may have an adverse effect on outcomes of kidney transplantation. The clinical outcomes of renal transplant recipients have significantly improved in recent years [3] and the scientific achievements of the last two-three decades have made it possible to improve the short-term graft survival [4].

Despite innovations in the field of immunology and modern diagnostic and therapeutic novelties in recent years, the main challenge remains the improvement of a long-term kidney transplant and recipient survival [5, 6]. The outpatient period is very

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important for long-term kidney transplant survival. The aim of our study was to analyze outpatient period complications after kidney transplantation and identify the factors during the outpatient period influencing kidney transplant and recipient survival.

Materials and Methods

This is a retrospective, observational study of cadaveric renal allograft recipients who were transplanted at our center between May 4, 2000, and December 31, 2013, and were followed until the end of May 2014. During this period, 277 transplantations were performed. The following groups of recipients were excluded from analysis: younger than 16 years (n = 8) and those whose data of late post-transplant period were missing (n = 5). There were 28 patients who lost their graft or died during the early post-transplant period. The final study sample consisted of 249 recipients. The patients were followed up until death, return to dialysis or until the end of the study (May 31, 2014).

Immunosuppressive therapy consisted of cyclosporine or tacrolimus plus steroids and MMF in all recipients, and daclizumab or basiliximab (at medium and high immunological risk groups) was used as induction therapy. Delayed graft function (DGF) was defined as a need for dialysis within the first week after kidney transplantation.

A detailed analysis of outpatient period complications was performed, including infectious, surgical, oncological, immunosuppressive and cardiovascular complications during the whole outpatient period, also considering the time after transplantation (first, second or third and subsequent years). The analysis did not include recipients who had not completed their full 2 or 3 years of follow-up after transplantation.

All analyses were performed using SPSS software. The groups were compared using the independent samples T-test and the chi-square test. The Z test was used to compare column proportions. Graft and recipient survival was estimated using the Kaplan-Meier survival method. The log-rank test was used to determine statistical differences in graft and patient survival between different variables. A two-sided *P*-value of 0.05 was considered to be statistically significant.

Results

Recipient and donor characteristics, graft and patient survival rates

The mean donor age was 42.5 ± 16.0 years (range, 7 to 75) with 64.3% of men. The main causes of donor death (cerebrovascular disease and trauma) distributed equally. The median time of cold ischemia was 20.00 hours (range, 9 to 32).

The average recipient age was 43.8 ± 11.8 years (range, 19 to 68) with 58.1% of men. DGF was observed in 22.9% of the recipients. Detailed donor and recipient characteristics are shown in Table 1.

Graft and patient survival rates are presented in Table 2.

Graft loss and patient death

Outpatient monitoring was carried out in 249 patients, of which 22 patients (8.8%) died and 27 patients (10.8%) returned to dialysis. The causes of recipient death of the whole outpatient period were: infection 31.8% (n = 7), cardiovascular events

Table 1. Donor and Recipient Characteristics

Characteristic	Mean ± SD/median (min – max) or %
Donors	
Age (years)	42.5 ± 16.0
Gender (male/female)	64.3/35.7
Cause of death	
cerebrovascular disease	47.5
trauma	49.4
others	3.1
History of hypertension (yes/no)	30.3/69.7
Terminal serum creatinine (umol/L)	90.50 (45–300)
Cold ischemia time (hrs)	20.00 (9 – 32)
Expanded criteria donor type (yes/no)	22.7/77.3
Recipients	
Age (years)	43.8 ± 11.8
Gender (male/female)	59.8/40.2
History of diabetes (yes/no)	13.7/86.3
Delayed graft function (yes/no)	22.9/77.1
Body mass index (kg/m^2)	24.22 (16.42 – 41.97)
Acute rejection in early postoperative period (yes/no)	10.0/90.0
Urinary tract infection in early post-transplant period (yes/no)	36.5/63.5
Human leucocyte antigen (HLA) mismatch	3.00 (0–6)

Table 2. Graft (overall and death-censored) and Recipient Survival Rates

Years after transplantation	Overall graft survival, %	Death-censored garft survival, %	Recipient survival, %
1 y	95.9	96.7	99.2
3 y	88.4	92.7	95.6
5 y	80.6	87.2	93.0
7 y	73.5	85.4	87.7
10 y	64.9	82.4	82.3

31.8% (n = 7), sudden death 18.2% (n = 4), other 9.1% (n = 2) and unknown reasons 9.1% (n = 2). The reasons for graft loss of the whole outpatient period were: chronic allograft nephropathy/recurrent glomerular diseases 42.8% (n = 13), infection 37.0% (n = 10), acute rejection 7.4% (n = 2) and others reasons 7.4% (n = 2). Until the end of the study, 200 recipients were followed with the functioning transplant kidney.

Outpatient period complications

Outpatient period complications were analyzed for total observation time (during the whole outpatient period), also considering the time after transplantation (first, second or third and subsequent years) (Table 3).

The most severe complication – **sepsis** – was diagnosed in 48 recipients (19.3%). Urinary tract was the gate of infection even in 79.2% cases of sepsis. Meanwhile, other sepsis gates included: postoperative wound (6.2%), central venous catheter (4.2%), and unknown gate (10.4%). Sepsis was statistically significantly more common during the first year after kidney transplantation compared with the second and third and subsequent years ($P < 0.05$).

The most frequent complications of the outpatient period were **urinary tract infections** (57.5%). The rate of urinary tract infections was

Table 3. Outpatient Period Complications and Comparison by the Year after Transplantation

Outpatient period complication	Total observation period (n = 249)	First year after transplantation (n = 249)	Second year after transplantation (n = 216)	Third and subsequent years after transplantation (n= 179)
	n (%)	n (%)	n (%)	n (%)
Urinary tract infection	143 (57.5)	110 (44.1)*	50 (23.2)*/ **	65 (36.3)**
Sepsis	48 (19.3)	29 (11.6)*	7 (3.2)*/**	19 (10.7)**
Pneumonia	38 (15.3)	12 (4.8)***	10 (4.6)**	20 (11.2)**/***
Acute rejection	30 (12.0)	20 (8.0)*/***	6 (2.8)*	5 (2.8)***
Oncological disease	15 (6.0)	4 (1.6)***	3 (1.4)**	8 (4.5)**/***
skin	7 (2.8)	1 (0.4)***	2 (0.9)	4 (2.2)***
prostate	2 (0.8)	–	–	2 (1.1)
lymphoproliferative system	1 (0.4)	–	1 (0.5)	–
other (testicles, kidney, iris)	4 (1.6)	3 (1.2)	–	1 (0.6)
several	1 (0.4)	–	–	1 (0,6)
Ureteral stenosis	18 (7.2)	15 (6.0)*/***	1 (0.5)*	2 (1.1)***
Lymphocele	20 (8,0)	20 (8,0)	–	–
Renal artery stenosis	3 (1,2)	2 (0,8)	1 (0,5)	–
Immunosupressive complications	116 (46.5)	73 (29.2)*	36 (16.1)*/**	43 (24.0)**
CyA toxicity	15 (6)	14 (5.6)***	7 (3.2)**	1 (0.6)**/***
CMV infection	36 (14.5)	22 (8.8)*/***	8 (3.7)*	8 (4.5)***
Polioma virus infection	4 (1.6)	2 (0.8)	2 (0.9)	–
Herpes virus infection	11 (4.4)	5 (2.0)	7 (3.2)	8 (4.5)
other virus infection	1 (0.4)	1 (0.4)	–	–
myelosuppression	10 (4.0)	10 (4.0)	–	–
diarrhea	5 (2.0)	3 (1.2)	2 (0.9)	2 (1.1)
post–transplant diabetes	2 (0.8)	–	–	2 (1.1)
gingival hyperplasia	6 (2.4)	–	4 (1.9)	7 (3.9)
hypertrichosis	2 (0.8)	1 (0.4)	2 (0.9)	–
hypertension	1 (0.4)	–	–	1 (0.6)
other	4 (1.6)	3 (1.2)	1 (0.5)	4 (2.2)
several	36 (14.5)	12(4.8)*	2 (0.9)*/**	10 (5.6)**
Cardiovascular complications	46 (18.4)	15 (6.0)*/***	6 (2.8)*/**	31 (17.4)**/***
myocardial infarction	10 (4.0)	1 (0.4)***	2 (0.9)**	7 (3.9)**/***
hypertensive crisis	4 (1.6)	1 (0.4)	–	3 (1.7)
heart rhythm disorders	8 (3.2)	4 (1.6)	2 (0.9)	5 (2.8)
stroke	7 (2.8)	3 (1.2)	1 (0.5)**	6 (3.4)**
other (heart failure exacerbation, angina pectoris and other)	17 (6.8)	6 (2.4)*/***	1 (0.5)*/**	10 (5.6)**/***

*$P < 0.05$, comparison of complications of the first and the second post-transplant year;
**$P < 0.05$, comparison of complications of the second and the third and subsequent post-transplant years,
*** $P < 0.05$, comparison of complications of the first and the third and subsequent post-transplant years.

higher in the first year after transplantation compared with the second and subsequent years.

Another severe complication was **acute rejection**. Two patients had 3 episodes of acute rejection, 3 recipients had 2 episodes and 25 recipients had 1 episode of acute rejection. Acute rejection was significantly more common during the first year after transplantation compared with subsequent years. Acute rejection was treated with methylprednisolone pulse therapy in 22 patients (73.3%), methylprednisolone pulse therapy, plasmapheresis, intravenous immunoglobulin in 3 patients (10.0%), strengthened or modified immunosuppression in 3 patients (10.0%), methylprednisolone pulse therapy and ATG in 1 patient (3.3%), and allograft nephrectomy due to life-threatening infectious complications in 1 patient (3.3%). The outcomes after acute rejection treatment were as follows: kidney function remained abnormal although deterioration has been stopped in 19 recipients (63.3%), deteriorated graft function in 2 recipients (6.7%), good treatment effect in 8 recipients (26.7%), and allograft nephrectomy in 1 recipient (3.3 %).

Oncological complications were significantly more common during the third and subsequent years after kidney transplantation compared with earlier years.

CMV infection was more common during the first post-transplant year comparing with the second and subsequent years. The number of CMV infection episodes per recipient ranged from 1 to 21. **CMV disease** (CMV virus detection and clinical symptoms) was diagnosed in 7 patients (2.8%). One CMV infection episode was identified in 4 recipients (1.6%), 2 episodes were identified in 2 recipients (0.8%), and 3 episodes in 1 recipient (0.4%).

Impact of outpatient period complications on graft and recipient survival

Graft survival. **Sepsis** diagnosed during the whole outpatient period was associated with worse overall graft survival (log-rank $P = 0.012$). In addition, sepsis diagnosed during the first post-transplant year was significantly associated with worse overall (log-rank $P < 0.001$) and death-censored **graft** survival (log-rank $P = 0.001$).

There was a significant correlation between **urinary tract infections** that occurred in the first post-transplant year and overall (log-rank $P = 0.024$) and death-censored (log-rank $P = 0.045$) **graft** survival.

The occurrence of **acute rejection** during the whole outpatient period was associated with poorer overall (log-rank $P = 0.032$) and death-censored (log-rank $P = 0.008$) **graft** survival.

Acute rejection diagnosed during the second post-transplant year and later affected the worse overall and death-censored graft survival (log-rank $P = 0.023$ and $P = 0.001$), too.

However, acute rejection diagnosed in the first post-transplant year had no association with overall (log-rank $P = 0.203$) and death-censored **graft** survival (log-rank $P = 0.161$).

The occurrence of **CMV infection** during the whole outpatient period and during the first post-transplant year had no association with worse overall (log-rank $P = 0.996$ and $P = 0.233$) and death-censored (log-rank $P = 0.293$ and $P = 0.395$) **graft** survival.

Pneumonia which occurred during the outpatient period was also significantly associated with overall graft survival (log-rank $P = 0.024$). Meanwhile, death-censored graft survival was not associated with pneumonia, oncological diseases, cardiovascular complications, sepsis, or urinary tract infections, regardless of the time of complications during the outpatient period.

Recipient survival. The occurrence of **sepsis** during the whole outpatient period and during the first year after transplantation was significantly associated with worse **recipient** survival (log-rank $P = 0.014$ and log-rank $P = 0.004$, respectively).

There was no significant correlation between acute rejection (log-rank $P = 0.932$), CMV infection (log-rank $P = 0.266$), pneumonia, oncological diseases, urinary tract infections and cardiovascular complications that occurred in the outpatient period and recipient survival.

Discussion

Outpatient period complications are assessed as factors that can affect both the recipient and the graft survival after kidney transplantation. Infectious complications were the most common complications of the outpatient period in our study. Urinary tract infections were diagnosed in more than a half of our patients and more often during the first year after kidney transplantation (44.1%). Urinary tract infections were significantly more frequent during the third and subsequent years after transplantation compared with the second post-transplant year. *Yalci et al.* analyzed first post-transplant year complications and established that in more than 60% of kidneys recipients at least 1 episode of infection was diagnosed [7]. Other authors reported the rate of infectious complications to be 50% and more [8, 9]. Urinary tract infection was the most common infectious complication in our study, the same as in other publications [7–11]. Besides, our results agree with a published rate of urinary tract infection (31–70%) during the first post-transplant year [7–12]. In our study, urinary tract infection was associated with worse graft survival and outcomes after kidney transplantation, as in previous publications [13, 14].

The incidence of pneumonia during the first post-transplant year in our kidney transplant recipi-

ents was low (only 4.8%). The rate of pneumonia, estimated by other authors, was in the rage of 5.2–18% [7–9, 12].

The most serious complication – sepsis – was diagnosed in 4–35% of the recipients during the first post-transplant year [7, 8, 11, 15, 16]. In our study, sepsis during the first-year post-transplant was diagnosed in 11.6% of the recipients and the main gate of infection was urinary tract. Sepsis was significantly negatively associated with overall (log-rank $P < 0.001$) and death-censored (log-rank $P = 0.001$) graft survival. Other researchers also noted that sepsis after kidney transplantation determined inferior allograft function [17]. Recipient survival was also negatively associated with sepsis (log-rank $P = 0.004$), as in other published papers [18, 19].

CMV infection is the most common viral complication after kidney transplantation. CMV infection affects the incidence of other infections [11], acute rejection [20], post-transplant graft function [11, 20] and graft survival [20, 21]. The rate of CMV infection is 10–46% [7, 11, 15, 20]. In our study, CMV infection was diagnosed in 14.5% and CMV disease in 2.8% of our recipients. There was no association with the recipient and graft survival (neither during the whole outpatient period nor in the first post-transplant year).

Acute rejection (during early and late post-transplant period) is negatively associated with graft survival compared with recipients without acute rejection [22]. Other authors reported that late acute rejection had an impact on inferior graft survival compared with early acute rejection [23, 24]; moreover, early acute rejection had no impact on late graft survival [25, 26]. *Dorje et al.* identified that a negative effect of late acute rejection on graft survival was related to young age, frequent nonadherence, or suboptimal immunosuppression and development of de novo donor-specific antibodies [24]. This could be explained by the increased immunogenicity of the young organism. Meanwhile, the decrease in the frequency of acute rejection in the first year after transplantation (even up to 5.8%) during the past decades is more likely to be related to the changes in immunosuppressive regimens [3]. Acute rejection was diagnosed in 12% of our recipients during the whole outpatient period and in 8% during the first post-transplant year. There was no association with recipient survival, but acute rejection had a negative effect on graft survival.

Ureteral stenosis is the most common (1.5–3%) surgical urological complication of the first post-transplant year [27–29]. The incidence of ureteral stenosis was 7.2% during the whole post-transplant period in our study. This complication was the most common (6.0%) during the first post-transplant year. *Frayek et al.* announced that implantation of ureteral stents after kidney transplantation was related to a decrease in ureteral complications [30], but may increase the rate of infectious complications [31].

The rate of cardiovascular complications after kidney transplantation may reach as much as 20% [32, 33], and acute coronary syndrome may reach 7–11% [34, 35]. Our results are similar to those of other authors.

We found that the rate of outpatient period complications was dependent on the time after transplantation. We did not find data in the scientific literature comparing the rate of post-transplant complications every next year. We compared the frequency of complications during the first, second, third and subsequent years after kidney transplantation and identified significantly more common urinary tract infections and sepsis (urinary tract being the infectious gate) during the first year compared with the second post-transplant year. We presume this difference could be determined by early urological complications (ureteral stenosis was significantly more frequent during the first year) and stronger immunosuppression during the first post-transplant year. However, we evaluated the rate of later urinary tract infections and established more frequent urinary tract infections during the third and subsequent post-transplant years compared with the second year. The same trends are observed in the evaluation of the rate of sepsis in the outpatient period. The frequency of pneumonia was significantly higher during the third and subsequent years, too. Possibly such an increase in infections during the third and subsequent post-transplant years is determined by a cumulation of more than one-year monitoring period. Acute rejection was significantly more common during the first post-transplant year compared with subsequent years in our recipients. However, oncological complications increase with time after transplantation [36] due to the use of immunosuppression [37], aging of recipients [37, 38] and viral infections [37, 39]. The incidence of CMV infection was higher during the first post-transplant year compared with the second and subsequent years in our recipients. Our rate of CMV infection was the same or lower as observed in recently published series [7, 20].

The main reasons for graft loss in our recipients were infectious complications, chronic allograft nephropathy, glomerular diseases and, in a few cases (7.4%), acute rejection. In *El-Zoghby's* study, fibrosis/atrophy accounted for one-third of the reasons for graft loss, glomerular disease for one-third, medical/surgical conditions (infection complications, non glomerular diseases) for 16%, acute rejection for 12%, and unknown reasons for 5% [40]. We observed a recurrence of primary kidney disease in only a few of our recipients, while graft loss due to this reason has been reported to reach as much

as 22% by other authors [41]. This difference can be explained by a brief observation after transplantation, considering that majority of the transplantations in our hospital were performed in the last 5–7 years. Transplanted kidney biopsies were not always performed due to the reason that end-stage graft failure and return to dialysis were determined by taking into account the history and the course of progression of graft failure.

Over the last two decades, patient survival after renal transplantation has been improved (ERA-EDTA 2013) [42]. As reported in other studies, overall mortality of recipients after kidney transplantation was 3–7.7% [12, 43]. The main causes of death after renal transplantation are infectious, cardiovascular complications and oncological diseases. Despite the fact that the incidence of infections due to improved surgical techniques, prophylaxis and immunosuppressive regimens tends to decrease [44], infection still remains one of the main factors influencing both the recipient and the graft survival and outcomes [12, 43], especially during the first post-transplantation year. Recipient mortality caused by infectious complications is in the range of 2–3.5% during the first year after kidney transplantation [12, 45]. The second common cause of death is cardiovascular events [43, 46]. *Farrugia with co-authors* found that 38.8% of recipients who had a history of myocardial infarction in the past died due to cardiovascular events during the first year after transplantation [43]. Our results agree with those recently discussed as the main reasons for mortality were infectious complications and cardiovascular events. We found that mortality in the first year after transplantation was 3.3%. In our study, about one-third of the causes of death with the functioning graft were cardiovascular events and one-third infectious complications, as in the recently published study of *McCaughan et al.* [41].

Conclusions

Infectious complications were the most common complications of the outpatient period. Urinary tract infections were diagnosed in more than a half of our patients after kidney transplantation. During the first year after transplantation, sepsis was diagnosed in 11.6% of the recipients and the main gate of infection was urinary tract. Acute rejection was diagnosed in 12% of our recipients during the outpatient period. Outpatient post-transplant period complications, such as sepsis, acute rejection, pneumonia and urinary tract infections (first year after transplantation), were significantly negatively associated with graft survival. Recipient survival was negatively associated with sepsis. The main reasons for graft loss in our recipients were infectious complications, chronic allograft nephropathy, and glomerular diseases. The main reasons for mortality after kidney transplantation were infectious complications and cardiovascular events.

Conflicts of interest: none

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