DOI: 10.15825/1995-1191-2024-1-20-25

EFFECT OF DELAYED GRAFT FUNCTION ON IMMEDIATE AND LONG-TERM KIDNEY TRANSPLANT OUTCOMES

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Objective: to analyze the immediate and long-term outcomes of kidney transplantation (KT) depending on the duration of delayed graft function (DGF). **Materials and methods.** The study conducted a retrospective analysis of KT outcomes in 312 patients operated on at Botkin Hospital from June 2018 to December 2022. Exclusion criteria were primary non-function, severe surgical complications that required emergency transplantectomy in the first week after KT and cases where a comprehensive approach to DGF prevention was applied. DGF was defined as the need for dialysis within the first 7 days of KT. The severity of this complication was assessed by the time it took the transplanted kidney function to normalize from mild DGF to severe. We analyzed the immediate and long-term outcomes of KT depending on the presence of initial function and the severity of DGF. **Results.** DGF developed in 25.3% of cases. The mean time for graft function normalization was 16.5 ± 6.8 days. Mild DGF occurred in 68% of cases, severe DGF was determined in the remaining cases (32%). The incidence of complications was statistically significantly higher in the severe DGF group: 14/25 (56%) *vs.* 15/54 (27.8%) ($p = 0.047$). There were also no significant differences in the rate of complications between recipients with immediate and mild DGF: 43/233 (18.4%) *vs.* 15/54 (27.8%) ($p > 0.05$). Severe DGF lasting for more than 2 weeks had a statistically significant association with postoperative complications ($p = 0.047$) and with decreased long-term graft survival (log-rank $p = 0.021$). **Conclusion.** Development of severe DGF mainly depends on donor characteristics, timing and peculiarities of graft preservation. Nevertheless, other factors, such as acute calcineurin inhibitor nephrotoxicity, should not be ignored. Therefore, prevention of all potentially modifiable risk factors for DGF should go hand in hand with the expansion of the indications for donation.

Keywords: kidney transplantation, delayed renal graft function, survival.

INTRODUCTION

KT is currently the most optimal modality of renal replacement therapy (RRT), as it is associated with the best long-term survival outcome and improved quality of life [1]. In this regard, the KT waiting list is steadily expanding in the world and in the Russian Federation, despite the annual increase in the number of transplants performed [2, 3]. This fact dictates the need for a constant expansion of the indications for deceased organ donation to increase the number of renal transplants. At the same time, this approach increases the risk of DGF, which leads to poorer immediate and long-term outcomes of KT [4].

DGF is defined as the need for RRT within 7 days after transplantation [5–6]. Many authors have noted a connection between DGF and several long-term adverse effects, including acute rejection, decreased graft survival and others [7–13], making the relevance of this problem extremely high. Our previous study demonstrated a statistically significant decrease in long-term survival of grafts that underwent delayed function. At the same time, DGF is certainly a multifactorial problem, and not all conditions falling under the classical definition of this complication may have an impact on early and long-term outcomes of KT. Thus, this paper is devoted to analyzing the immediate and long-term outcomes of KT depending on the duration of DGF.

MATERIALS AND METHODS

The study was based on a retrospective analysis of KT outcomes in 312 patients operated at Botkin Hospital from June 2018 to December 2022. Patients with primary non-function were excluded, as well as those with severe surgical complications that required urgent graftectomy in the first week after KT. Since mid-2022, a set of measures aimed at preventing DGF has been proposed and implemented in our hospital. It allowed us to significantly reduce the burden and slightly change the structure of risk factors for this complication. In order to exclude errors in interpretation of the results of this analysis, cases where a comprehensive approach to DGF prevention was applied, were also excluded.

Mean recipient age was 46.02 ± 11.5 (22 to 67) years. There were 196 (62.8%) men, 116 (37.2%) women. Most

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of the patients were on RRT: 212/312 (67.9%) were on hemodialysis, 38/312 (12.2%) were on peritoneal dialysis; and 15 patients (4.8%) were operated on before RRT was initiated. Among the causes of end-stage kidney disease, chronic glomerulonephritis was predominant – in 173/312 (55.4%). Also, 26/312 (8.3%) had diabetic nephropathy, 25/312 (8%) had chronic tubulointerstitial nephritis, 15/312 (4.8%) had chronic pyelonephritis, and 9/312 (2.8%) had a renoprival condition and 64/312 had other diseases (20.5%).

Isolated KT from a deceased donor was performed in all cases. Mean donor age was 48.35 ± 10.2 (18 to 71) years. In 163 (52.2%) cases, the donor was considered a standard donor, 137 (43.9%) cases used expanded criteria donors, and 12 (3.8%) cases used grafts obtained from donors with irreversible circulatory arrest. Mean donor ICU stay was 61.7 ± 37.2 (95% CI: 36.9–86.5) hours and mean cold preservation time was 11.3 ± 4.9 (95% CI: 10.1–13.3) hours.

Kidney removal, kidney transplantation, management of recipients in the early postoperative period, and selection of immunosuppressive therapy were all done in accordance with standard protocols of the National Clinical Guidelines. DGF was defined as the need for hemodialysis within 7 days after surgery. The severity of this complication was assessed by the time it took to normalize graft function. In this work, we used the following gradation: mild DGF (≤14 days) and severe DGF (≥15 days). We analyzed the immediate and long-term outcomes of KT depending on initial graft function and DGF severity.

Statistical processing and data analysis

Statistical processing and data analysis were performed in the SPSS Statistics program for Microsoft Windows version 26 (USA). Student's t-test or Welch's t-test was used to compare two groups of quantitative data in the normal distribution (depending on the equality of variances). When distribution differs from normal, the Mann–Whitney U-test was used to compare two groups of quantitative data, and the Kruskal–Wallis test was used to compare three or more groups. Qualitative indicators were compared using Pearson's chi-squared test or Fisher's exact test with determination of the odds ratio (OR) and closeness of association of the studied features. Survival analysis was performed using the Kaplan–Meier estimator with determination of statistically significant differences using the Cox–Mantel log-rank test. Differences were considered statistically significant at $p < 0.05$, the trend toward statistical significance was defined as $p < 0.1$.

RESULTS

Of the 312 cases retrospectively selected for this analysis, DGF occurred in 79 (25.3%). The mean time to normalization of graft function was 16.5 ± 6.8 (95% CI: 10.2–21.7) days. According to the above grading of DGF severity, 54/79 cases (68%) were determined to have mild DGF, and the remaining cases had severe DGF (25/79, 32%).

In 72/312 (23.1%) cases, surgical complications of varying severity developed in the early postoperative period. Postoperative wound hematoma, requiring revision, developed in 18/312 (5.7%) cases, lymphocele requiring intervention in 25/312 (8%), wound infection in 27/312 (8.6%), urological complications in 11/312 (3.5%), pneumonia in 6/312 (1.9%), and sepsis in 15/312 (4.8%) recipients. In 23/312 (7.3%) patients, two or more complications simultaneously (or sequentially) were recorded in the early postoperative period. In 7 cases, these complications led to graft loss, in 3 of which the cause was in-hospital recipient mortality. DGF increased the chances of surgical complications by 2.56 (95% CI: 1.5–4.5) times ($p = 0.001$). The rate of complications was statistically significantly higher in the severe DGF group: 14/25 (56%) versus 15/54 (27.8%) in mild DGF ($p = 0.047$). It should be noted that we did not find statistically significant differences in the incidence of complications between recipients with immediate and mild delayed function: 43/233 (18.4%) vs. 15/54 (27.8%) ($p > 0.05$). Immediate KT outcomes depending on initial graft function are clearly presented in Table.

One-year kidney graft survival in a group of 312 recipients was 92.4% (95% CI: 88.1–96.3%) and four-year survival was 74.0% (95% CI: 63.2–81.2%). DGF worsened the long-term outcomes of KT statistically significantly, with cases of death of a recipient with a functioning graft censored. Thus, the 1- and 4-year survival rates were 99.4% (95% CI: 91.3–100%) and 95.5% (95% CI: 82.3–98.1%) for immediate graft function, and 94.8% (95% CI: 87.4–97.2%) and 83.6% (95% CI: 71.1–92.4%) for DGF (log-rank $p = 0.001$). However, long-term survival between immediate function and mild DGF recipients was not statistically significantly different ($p > 0.05$). In contrast, long-term graft survival for severe DGF was statistically significantly lower (log-rank $p = 0.021$) than immediate function. The 1- and 3-year graft survival rates for severe DGF were 79.4% (95% CI: 69.2–85.4%) and 53.0% (95% CI: 26.5–71.2%), respectively. The main causes of graft loss in the severe DGF group, in addition to recipient death for reasons unrelated to the transplanted kidney, were infectious complications 16/25 (64%) and acute rejection 9/25 (36%). An analysis of graft survival depending on initial function is presented in Figure.

DISCUSSION

Our study once again emphasizes the extreme urgency of the problem of DGF. An expansion of criteria for deceased donation following the disproportionate increase in transplant demand will inevitably lead to higher incidence of this complication. Nevertheless, as

mentioned above, it is no secret that the DGF problem is multifactorial in nature. Our previous studies identified the main risk factors of DGF under which we proposed a set of preventive measures aimed at improving graft function in the early postoperative period.

The classical dialysis-based definition of DGF has been criticized by many authors [14]. Indeed, a number of factors may lead to the need for RRT in the first week after surgery but have nothing to do with the severity of ischemia-reperfusion injury (IRI), the morphologic basis of DGF. The most prominent examples include oligoanuria in the recipient before KT, acute rejection, or calcineurin inhibitor nephrotoxicity occurring immediately after KT. Nevertheless, a better definition has not been presented to date. In our opinion, the classical definition represents a standard that is convenient for statistical processing and subsequent analysis of outcomes, but it requires refinement.

To date, there is no unequivocal answer in the world literature as to whether the presence of DGF affects long-term survival. In an attempt to justify the expansion of criteria for deceased kidney donation, some authors claim comparable long-term survival regardless of initial function. Others, on the contrary, demonstrate increased risks of complications and graft loss in the presence of DGF.

In an attempt to clarify these contradictions, we once again retrospectively analyzed our own renal transplant

Table

Immediate kidney transplant outcomes depending on DGF

Indicator	Immediate function (A) (n = 233)	Mild DGF (B) (n = 54)	Severe DGF (C) (n = 25)	p
Recipient's age (years)	44 (IQR: 32–58)	45 (IQR: 40–52)	49 (IQR: 44–59)	0.14
Recipient's BMI (kg/m^2)	25 (IQR: 22.5–28)	26 (IQR: 24–28)	26 (IQR: 23.7–30.5)	0.51
Cold preservation time (minutes)	680 (IQR: 570–820)	710 (IQR: 670–850)	820 (IQR: 721–900)	A-C < 0.001 B-C < 0.001
Donor age (years)	47 (IQR: 38–56)	46 (IQR: 40–52)	57 (IQR: 48–59)	A-C = 0.018 B-C = 0.035
Donor BMI (kg/m^2)	26 (IQR: 24–29)	27.8 (IQR: 25–31)	31 (IQR: 26–33)	A-C = 0.032 B-C = 0.044
Median duration of DGF	0	7 (IQR: 3–9)	25 (IQR: 19–35)	A-C < 0.001 B-C < 0.001
Highest tacrolimus trough levels (C_0) in the first 7 days	12.4 (IQR: 9.2–13.4)	22.2 (IQR: 16.2–24.4)	20.6 (IQR: 15.2–26.4)	A-B = 0.03 A-C = 0.014
Rate of postoperative complications	43/233 (18.4%)	15/54 (27.8%)	14/25 (56%)	A-C = 0.02 B-C = 0.017

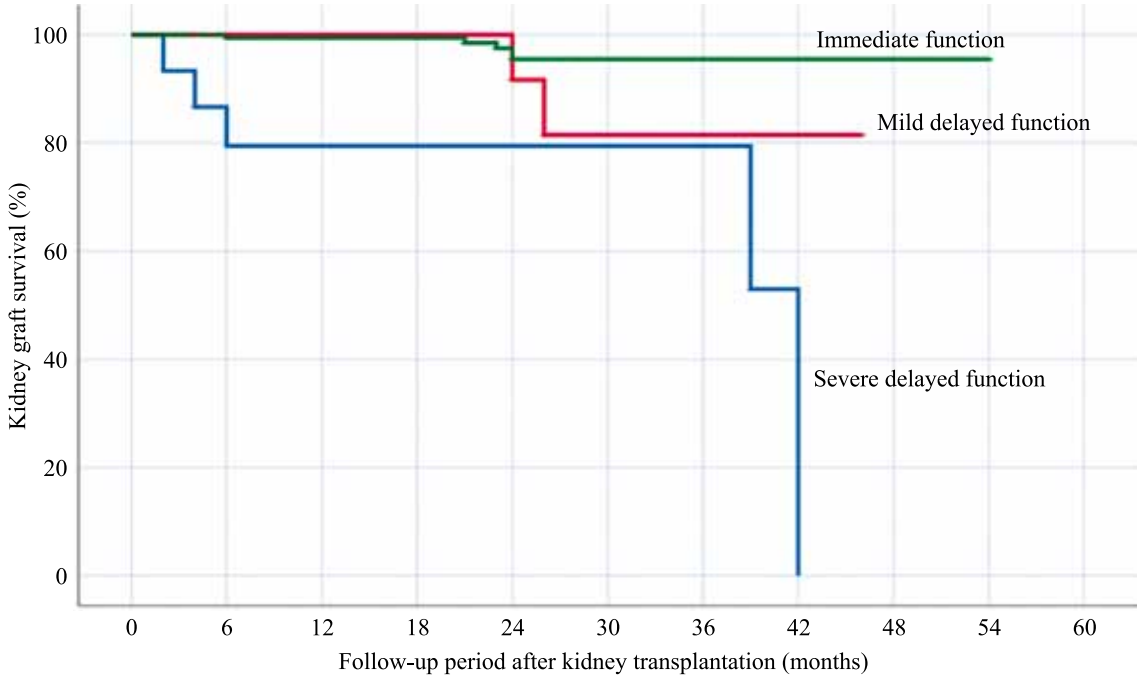

Fig. Long-term survival of kidney grafts depending on initial function

outcomes. In our opinion, DGF duration could be a clarifying indicator that can at least indirectly separate truly severe IRI from the transient need to put the recipient on dialysis. Indeed, DGF >2 weeks had a statistically significant association with postoperative complications ($p = 0.047$), as well as with lower long-term graft survival (log-rank $p = 0.021$). In our opinion, severe DGF is mainly influenced by donor characteristics, timing and peculiarities of graft preservation. Nevertheless, other factors, such as acute calcineurin inhibitor nephrotoxicity, should not be ignored. While their presence in KT from a standard donor is unlikely to lead to long-term DGF, in KT from an expanded criteria donor, they may significantly exacerbate this complication and sometimes lead to irreversible injury to the transplanted organ. Thus, prevention of all potentially modifiable risk factors for DGF should go hand in hand with expansion of donor criteria.

The authors declare no conflict of interest.

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The article was submitted to the journal on 05.08.2023