

## **Risk factors for delayed kidney graft function from a deceased donor**

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### **Abstract**

**Aim.** *To determine statistically significant risk factors for delayed renal graft function. To assess the impact of delayed kidney graft function on the development of other complications, graft and recipient survival.*

**Material and methods.** *In 237 consecutive kidney transplant recipients (from June 2018 to December 2021), we assessed its function in the early postoperative period. Delayed function was considered to be the need for hemodialysis in the first week after surgery. Among the donor factors, the type of donor, age, body mass index, the presence of vasopressor support, the time the donor was in intensive care, and the maximum level of creatinine during the follow-up were evaluated. Recipient risk factors include age, gender, body mass index, presence/absence and amount of urine, presence of preformed anti-HLA antibodies and/or repeated kidney*

transplantation, number of mismatches for six HLA antigens, number of mismatches for HLA-DR, presence and type of renal replacement therapy, etiology of end stage kidney disease. Among the perioperative risk factors are the duration of cold preservation, the time of second warm ischemia, the volume of intraoperative blood loss, the intraoperatively determined renal arterial resistive index of the renal graft, and the maximum concentration of tacrolimus in the first 4 days after kidney transplantation. After that, the relationship between the presence of delayed kidney graft function and the development of early postoperative complications was assessed and its effect on the long-term survival of grafts and recipients was analyzed.

**Results.** Out of 237 cases, 9 showed no function of the transplanted kidney, and therefore the grafts were removed. The incidence of delayed renal graft function was 24.5% (58/237). According to the results of a univariate analysis, a statistically significant relationship of a delayed renal graft function was found to the following parameters: donor body mass index ( $p=0.019$ ), male gender of the recipient ( $p=0.048$ ), recipient body mass index ( $p=0.038$ ), amount of urine ( $p=0.003$ ), anuria ( $p=0.002$ ), presence of preformed antibodies ( $p=0.025$ ), repeated transplantation ( $p=0.002$ ), time of second warm ischemia ( $p=0.036$ ), intraoperative renal arterial resistive index ( $p=0.004$ ) and maximum tacrolimus concentration in the first 4 days ( $p=0.022$ ). In the multivariate model, donor body mass index  $>30 \text{ kg/m}^2$  and peak tacrolimus concentration  $>23 \text{ ng/mL}$  in the first 4 days were statistically significant ( $p=0.018$  and  $p=0.025$ , respectively). A trend towards statistical significance was noted in the presence of oligoanuria before kidney transplantation ( $p=0.066$ ) and resistance index  $>0.75$  after surgery ( $p=0.056$ ). One-year renal transplant survival in the absence and presence of delayed kidney graft function was 92.4% and 87.7%, two-

year survival was 89.4% and 76.1%, respectively. The effect of a delayed kidney graft function on graft survival was statistically significant ( $p=0.01$ ), while the overall recipient survival did not differ between the groups.

**Conclusion.** During the univariate analysis, we identified 9 statistically significant factors, of which at least 3 are potentially modifiable. In the multivariate model, the most significant modifiable risk factor was an increased concentration of tacrolimus, which prompted the authors to reconsider the existing immunosuppressive protocol at the City Clinical Hospital n.a. S.P. Botkin. We consider the search for modifiable statistically significant risk factors for patients, their analysis and the implementation of preventive measures to be important tasks for each kidney transplant center.

**Keywords:** kidney transplantation, delayed kidney graft function, risk factors

**Conflict of interests** Authors declare no conflict of interest

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AKI – acute kidney injury

BMI – body mass index

CKD – chronic kidney disease

CRF – chronic renal failure

DKGF – delayed kidney graft function

IRI – ischemia-reperfusion preservation graft injury

KT – kidney transplantation

OR – odds ratio  
RI – resistance index  
RRT – renal replacement therapy  
SWI – second warm ischemia  
US – ultrasonography/ultrasound examination

## **Introduction**

With current development of medicine, kidney transplantation (KT) is the "gold standard" for the treatment of the end-stage renal disease, since it demonstrates the best medical, social and economic efficiency in patients without absolute contraindications to this intervention [1]. Delayed kidney graft function (DKGF) according to the world literature is one of the most common complications of the early postoperative period. It is undeniable that the increase in DKGF incidence has mainly been associated with an increase in the donor pool due to the expansion of the criteria. Thus, the incidence of DKGF makes a mean of 5–10% in living donor KT, 15–35% in KT from a donor with a confirmed brain death, and about 50% in KT from a donor with an irreversible arrest of effective blood circulation [2–7].

Delayed kidney graft function represents acute kidney injury (AKI), however, is not defined as a 2-fold increase in serum creatinine within 48 hours, but as the need for renal replacement therapy (RRT) within 7 days after transplantation. For use in clinical practice, this definition is not perfect, but at the same time it provides the standard convenient for statistical processing, according to which transplant centers can pragmatically report their own results [8]. It should be noted that the delayed kidney/renal graft function is a risk factor for many long-term adverse consequences of KT, including acute rejection, reduced

graft survival, and others [9–14]; and therefore the relevance of this problem is extremely high.

Despite the obvious impact of donor characteristics on the DKGF development, the structure of risk factors for this complication is extremely diverse. Along with donor risk factors such as: donor age over 60 years, donor body mass index (BMI) over 30 kg/m<sup>2</sup>, donation after cardiac death, AKI presence, high level of vasopressor support, etc. [15–19], the risk factors on the recipient's part play an important role. With different levels of evidence, they include an increased BMI, male gender, dialysis duration, absence of residual diuresis, sensitization to HLA antigens and/or repeated KT, the number of HLA-DR mismatches, a history of diabetes mellitus, cardiovascular pathology, etc. [20–23]. Perioperative risk factors, including prolonged periods of static cold preservation [24–26], duration of primary [27, 28] and secondary warm ischemia [29], may also have a certain impact on DKGF development. Some authors noted the role of the nephrotoxic effect of calcineurin inhibitors in the early postoperative period as the cause of the DKGF development [30, 31]. To date, there are limited data on the effect of the recipient's hypercoagulation status on the decrease in the initial function of the kidney graft [32].

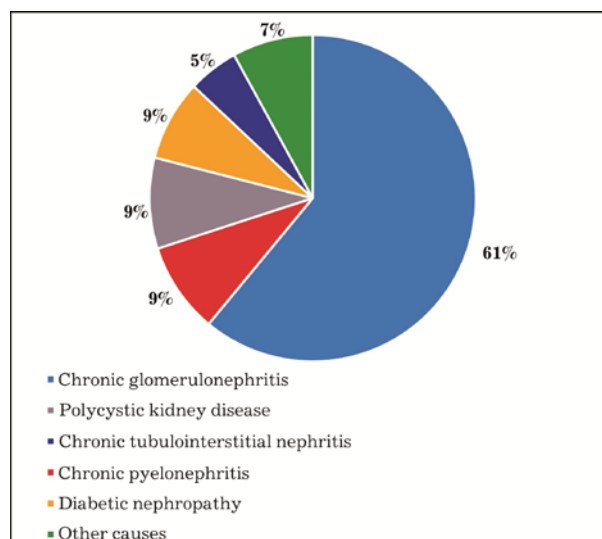
In the course of studying the literature, we noted differences in detected statistical significance of the same risk factors for DKGF in different authors. In this regard, the main goal of our study was to analyze potential risk factors and the impact of delayed kidney graft function on long-term adverse effects in kidney transplant recipients operated on at our center from 2018 to 2021.

## Material and methods

From June 2018 to December 2021 at the City Clinical Hospital n.a. S.P. Botkin 237 isolated KT from a post-mortem donor were performed.

### *Characteristics of recipients*

Among all recipients, there were 147 (62%) men and 90 (38%) women. The mean age of the patients was  $46.69 \pm 11.55$  (from 19 to 73) years. The most common cause (61%) of the end-stage chronic renal failure (CRF) was chronic glomerulonephritis (Fig. 1).



**Fig. 1. Etiological structure of end-stage chronic renal failure in kidney transplant recipients**

At the time of KT, 226 of 237 patients were on RRT, of which 185 (82%) were treated with program hemodialysis, 41 with peritoneal dialysis (18%). Diuresis before surgery was noted in 158 patients (66.6%), and was absent in 79 (33.4%). The performed KT was the first one in 203 patients (85.7%), the second one in 32 (13.5%), and the third one in 2 (0.8%). The median BMI of the recipients was 25.65 (IQR: 23–

29) kg/m<sup>2</sup>. An increase in the level of preexisting class I antibodies was observed in 15 patients (6.3%), those of class II in 18 patients (7.6%).

#### *Donor characteristics*

In all 237 cases, KT was performed from a post-mortem donor. The kidney donor was qualified as a standard criteria donor in 119 cases (50.2%), as an expanded criteria donor in 115 cases (48.5%), as a donor with a cardiac arrest in 3 cases (1.3%). Median donor age was 49 (IQR: 41–55) years, BMI was 26.8 (IQR: 24.3–31.0) kg/m<sup>2</sup>. Median creatinine levels and ICU length of stay were 86.5 (IQR: 70–103) µmol L and 49 (IQR: 30.5–77.0) hours, respectively. Vasopressor support was required in 202 of 237 donors (85.2%), among whom 16/202 (7.9%) had a dose of norepinephrine that either exceeded 1000 ng/mg/mL or required the use of a second vasopressor drug.

#### *Characterization of perioperative factors*

Kidney removal from the donor, cold preservation, surgery on the recipient, recipient management in the postoperative period and immunosuppressive therapy were performed using standard methods according to the National Clinical Guidelines. In all cases, Custodiol® HTK Solution was used to preserve kidney grafts. The median cold storage time was 10.4 (IQR: 8.5–12.3) hours. The median time of second warm ischemia (the formation of vascular anastomoses) was 40 min (IQR: 30–50). Mean operative time and intraoperative blood loss were 237.1±43.6 min (95% CI: 231.5–242.7) and 126.5±72.7 (95% CI: 117.1–136.0) mL. In 188 of 237 cases, we performed intraoperative ultrasound (US) Dopplerography of the renal graft with measuring the resistance index (RI) of arterial blood flow, which median was 0.7 (IQR: 0.6–0.73). As an immunosuppressive therapy in the early postoperative period, a

triple-component regimen was used in all cases, consisting of tacrolimus of extended release, mycophenolic acid derivatives, and methylprednisolone. Basiliximab was used for induction in all cases intraoperatively and on the 4<sup>th</sup> day. Methylprednisolone, 500 mg intravenously, was also administered intraoperatively, on the 3<sup>rd</sup>, and 5<sup>th</sup> days. The starting dose of tacrolimus that the patient took before surgery was determined at the rate of 0.2 mg/kg. The target concentration of tacrolimus in the early postoperative period was considered to be 8–15 ng/mL.

#### *Methods and statistical analysis*

In 237 kidney transplant recipients, we evaluated the renal graft function in the early postoperative period. Delayed function was defined as the need for hemodialysis in the first week after surgery. Based on our own data, we performed a retrospective analysis of possible risk factors for the development of DKGF. The analysis of its risk factors and long-term graft survival included all kidney transplant recipients, excluding the patients with developed primary graft non-function and severe surgical complications that required urgent graftectomy in the early postoperative period.

We evaluated the following donor factors: the donor type, age, BMI, the presence of vasopressor support, the time of donor stay in the intensive care unit, and the maximum level of creatinine during the follow-up. Among the risk factors on the recipient's part we evaluated the age, gender, BMI, the presence/absence and amount of residual urine, the presence of pre-existing anti- HLA antibodies and/or repeated KT, the number of mismatches for six HLA antigens, the number of mismatches for HLA-DR, the presence of and type of RRT, the etiology of the end-stage chronic renal failure. The assessed perioperative risk factors were



the following: the duration of cold preservation, the time of second warm ischemia (SWI), the intraoperative blood loss volume, the RI of the arterial blood flow in the kidney graft determined at the surgery completion, and the highest tacrolimus C<sub>0</sub> in the first 4 days after KT (Table 1). At the final stage of the study, we assessed the relationship between the presence of DKGF and the development of early postoperative complications, and also analyzed the impact on the long-term graft and recipient survival rates.

**Table 1. Potential risk factors and predictors of delayed kidney graft function**

From the donor	Perioperative	From the recipient
<ul style="list-style-type: none"> <li>– Donor Type (Standard/Expanded Criteria)</li> <li>– Age</li> <li>– BMI</li> <li>– Need for vasopressor support</li> <li>– Dose of norepinephrine over 1000 ng/kg/mL and/or connection of a second vasopressor</li> <li>– Time of stay in the intensive care unit</li> <li>– Maximum creatinine level</li> </ul>	<ul style="list-style-type: none"> <li>– SWI time</li> <li>– Intraoperative blood loss volume</li> <li>– Intraoperative RI</li> <li>– Maximum tacrolimus C<sub>0</sub> in the first 4 days after KT</li> </ul>	<ul style="list-style-type: none"> <li>– Age</li> <li>– Gender</li> <li>– BMI</li> <li>– Residual diuresis</li> <li>– Anuria</li> <li>– Sensitization to HLA antigens</li> <li>– Re-transplantation</li> <li>– Number of mismatches for 6 HLA antigens</li> <li>– HLA - DR mismatches</li> <li>– Presence of RRT</li> <li>– Type of RRT</li> <li>– CKD Etiology</li> </ul>

Note: CKD, chronic kidney disease

Statistical processing and data analysis were performed using the SPSS Statistics software for Microsoft Windows, version 26 (USA). At the first stage, a univariate analysis of possible risk factors for DKGF was performed. To compare two groups of quantitative data with a normal

distribution (depending on the equality of variances), either Student's t-test or Welch's t-test was used. With a distribution that differed 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. Comparison of qualitative variables was made using Pearson's  $\chi^2$ -test or Fisher's exact test with the determination of the odds ratio (OR) and the correlation of the studied features. Differences were considered statistically significant at  $p < 0.05$ , the trend towards statistical significance was defined as  $p < 0.1$ . Dichotomization of statistically significant quantitative risk factors was performed with the determination of the cut-off point by using ROC-analysis, followed by the comparison of the obtained binary variables depending on the presence of DKGF. Statistically significant risk factors for DKGF were analyzed in a multivariate binary logistic regression model. Survival analysis was performed using the Kaplan-Meier method with the determination of statistically significant differences using the Mantel-Cox Longrank test.

## **Results**

In 9 of 237 cases, the absence of transplanted kidney function was recorded: the presence of a primary graft non-function was diagnosed in 2 cases (0.8%), vascular complications on the first day after surgery were seen in 7 cases (2.9%), and therefore the grafts were removed. The incidence of DKGF was 24.5% (58/237). In the course of a univariate analysis, we did not find a statistically significant association of DKGF with the donor type, age, the need for vasopressor support, the dosage of vasopressors (including at a dosage of norepinephrine more than 1000 ng/kg/mL or the presence of a second vasopressor), the maximum level of creatinine and the time of donor's stay in the intensive care unit ( $p > 0.05$ ). With regard to the DKGF presence, the groups did not statistically

significantly differ in recipient's age, the number of HLA-antigen mismatches (including HLA-DR), the presence and type of RRT, and the CKD etiology ( $p>0.05$ ). At the same time, the recipient's renoprival state before KT, in contrast to other causes of CKD, was statistically significantly associated with DKGF ( $p=0.02$ ). Among the perioperative factors, the intraoperative blood loss volume did not show a significant relationship to DKGF ( $p>0.05$ ).

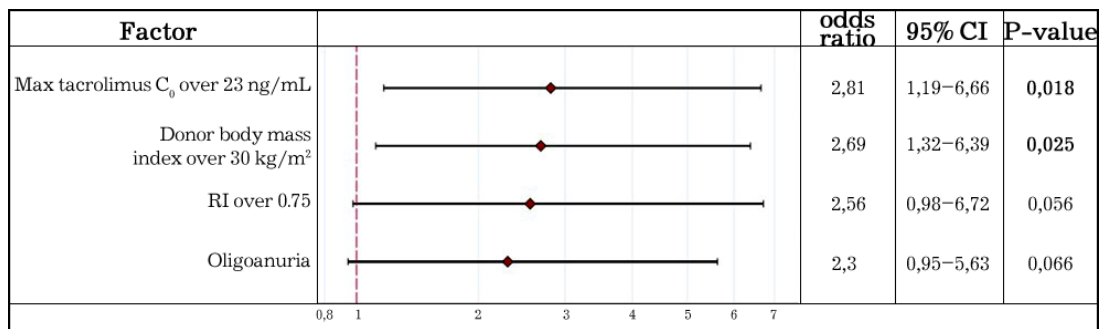
On the contrary, according to the results of a univariate analysis, there was a statistically significant relationship to DKGF development from donor's BMI ( $p=0.019$ ), recipient's male gender ( $p=0.048$ ), recipient BMI ( $p=0.038$ ), amount of residual urine ( $p=0.003$ ), anuria ( $p=0.002$ ), presence of pretransplant antibodies ( $p=0.025$ ), retransplantation ( $p=0.002$ ), second warm ischemia time ( $p=0.036$ ), intraoperative arterial blood flow resistance index KT ( $p=0.004$ ), and the peak tacrolimus concentration in the first 4 days ( $p=0.022$ ). Dichotomization was performed for statistically significant quantitative factors. Thus, new variables were obtained: donor BMI  $> 30 \text{ kg/m}^2$ , oligoanuria (urine  $< 250 \text{ ml/day}$ ), SWI time  $> 45 \text{ min}$ , RI  $> 0.75$ . All these variables had also a statistically significant relationship to DKGF development ( $p < 0.05$ ), but of weak (V Cramer: 0.1-0.2) or moderate (V Cramer: 0.2-0.4) correlation. The results of univariate analysis are presented in Table 2.

**Table 2. Statistically significant risk factors for delayed kidney graft function development (univariate analysis)**

Risk factor	DKGF incidence				p-value	OR; 95% CI	V Cramer
	Presence of a factor		Absence of a factor				
	n	%	n	%			
Donor risk factors							
Donor BMI>30 kg/m <sup>2</sup>	25/73	34.2	30/143	21.0	0.034	1.96; 1.05–3.68	0.144
Recipient risk factors							
Sensitization	11/25	44	41/186	22	0.025	2.78; 1.17–6.58	0.165
Recipient BMI>25 kg/m <sup>2</sup>	38/125	30.4	17/94	18.1	0.038	1.98; 1.03–3.79	0.141
Male gender	42/139	30.2	16/87	18.4	0.048	0.52; 0.27–1.00	0.132
Oligoanuria	28/73	38.4	30/153	19.6	0.003	2.56; 1.38–4.73	0.201
Perioperative predictors and risk factors							
Operation time >245 min	29/84	34.5	29/140	20.7	0.022	2.02; 1.10-3.71	0.153
SWI time >45 min	22/61	36.1	35/158	22.2	0.035	1.98; 1.04-3.77	0.142
RI>0.75	17/35	48.6	26/144	18.1	<0.001	4.29; 1.95-9.42	0.283
Maximum tacrolimus C <sub>0</sub> >23 ng/mL	33/93	35.5	25/123	20.3	0.013	2.16; 1.17-3.97	0.169

Notes: 95% CI, 95% confidence interval; C<sub>0</sub>, zero concentration in the first 4 days

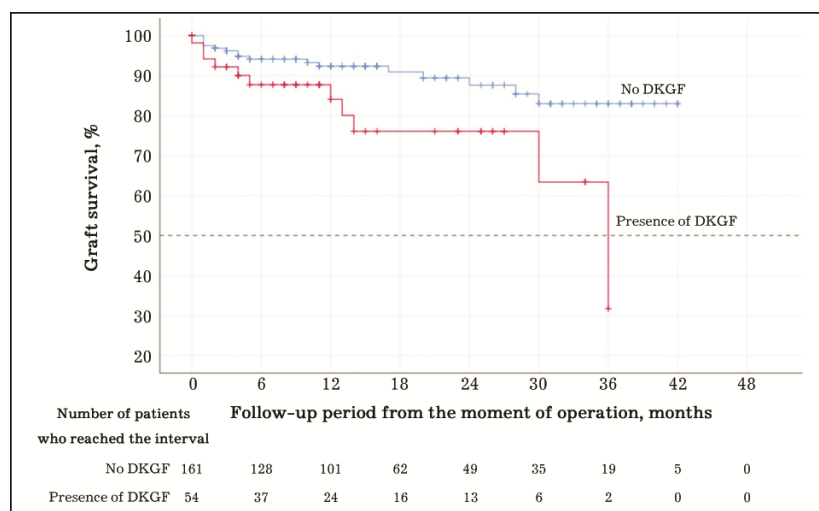
According to the results of multivariate analysis, which included factors from Table 1, the donor's BMI >30 kg/m<sup>2</sup> and the highest tacrolimus C<sub>0</sub> in the first 4 days >23 ng/mL (p=0.018 and p=0.025, respectively) achieved statistical significance. A trend towards statistical significance was noted for the following factors: oligoanuria (p=0.066) and RI >0.75 (p=0.056). The results of multivariate analysis are presented in Fig. 2.



**Fig. 2. Multivariate analysis of risk factors for delayed kidney graft function**

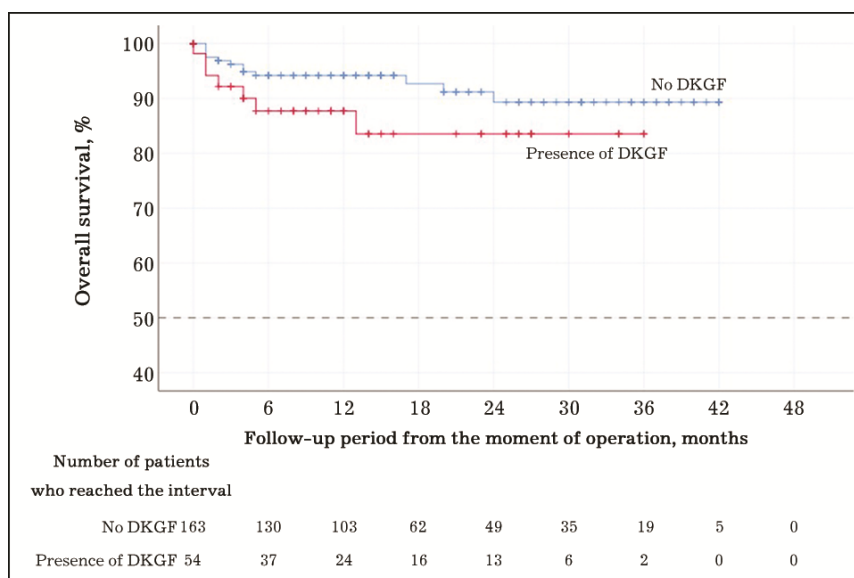
When analyzing the impact of DKGF on the development of all complications in the early postoperative period, no statistically significant relationship was found, however, a trend towards statistical significance was observed in an increased incidence of infectious complications in the presence of DKGF (10/24; 58.8% vs. 7/36; 41.2 %,  $p=0.061$ ). An increase in the rate of infectious complications in the early postoperative period was also associated with an increased tacrolimus concentration in the first 4 days, as an independent risk factor for DKGF in our patients ( $p=0.047$ ).

One-year kidney graft survival rates in the absence and presence of DK/RGF were 92.4% (95% CI: 88.0-96.8%), and 87.6% (95% CI: 80.8-94.4%), those for two years made 84.1% (95% CI: 72.5–95.7%) and 76.1% (95% CI: 61.4–91.1%), respectively (Fig. 3). The impact of DKGF on the graft survival was statistically significant ( $p=0.011$ ). The causes of graft death in our recipients were: death of a recipient with a functioning graft in 17/36 (47.3%), infectious complications in the early postoperative period in 9/36 (25.0%), rejection in 7/36 (19.4%), and other causes in 3/36 (8.3%).



**Fig. 3. Survival of grafts depending on the presence of delayed kidney graft function. Kaplan-Meier curves**

One-year overall recipient survival rates in the absence and presence of DKGF were 94.2% (95% CI: 91.2-97.2%) and 87.7% (95% CI: 78.3-96.1%), those for two years were 89.3% (95% CI: 82.7–95.9%) and 83.5% (95% CI: 71.3–95.7%), respectively (Fig. 4). The impact of DKGF on the overall survival was not statistically significant ( $p=0.134$ ). In the overall structure of mortality causes in kidney transplant recipients, the main ones were SARS-Cov-2-caused pneumonia in the first year and a half after KT in 9/22 (41%), infectious complications of another etiology and sepsis in 8/22 (36%), acute myocardial infarction in 2/22 (9%), and others in 3/22 (14%).



**Fig. 4. Overall survival of recipients depending on the presence of delayed kidney graft function. Kaplan-Meier curves**

## Discussion

Reviewing the data from the world literature and our own experience, we can confidently say that the delayed function of the kidney graft is a common complication with an extremely diverse structure of risk factors for it. KT is the only chance for a patient with end-stage renal disease to return to a full life. At the present stage of medicine development, it has become possible to reduce the requirements for the candidate selection, which allows more patients to get on the waiting list. In this regard, the need for donor organs is steadily increasing every year throughout the world. Expanding the criteria for organ donation is a forced, but certainly justified step towards increasing the availability of transplant care. Unfortunately, the development of a DKGf is highly dependent on conditionally non-modifiable risk factors from both the donor and recipient.

At the same time, the identification of potentially modifiable factors influencing the DKGF development is an important task for transplantologists around the world. However, it is extremely difficult to conduct studies aimed at finding the statistical significance of one or another risk factor for DKGF, given the polyetiological nature of this complication. Such work usually requires a large number of cases and the exclusion of the impact of other potentially confounding factors. Analyzing the results obtained by different authors, we noted differences in the identified significant risk factors for delayed graft function. Most likely, along with other limitations of single-center retrospective studies, this was due to differences between recipients, donors, treatment approaches, etc., which prompted us to look for potentially modifiable factors influencing the development of DKGF in our patients.

**Univariate analysis.** In a univariate analysis, we identified 9 factors that were statistically significantly related to the DKGF development. Notable is a low correlation determined independently for each factor by V-Cramer value. This probably means that such factors as prolonged time of second warm ischemia, total surgery duration, etc., are not decisive, but they can have a significant impact on the combination of factors that increase the risk of DKGF development.

*The second warm ischemia time of more than 45 minutes.* Second warm ischemia is one of the most critical periods for a kidney graft. Many authors have noted a statistically significant relationship between the time of making vascular anastomoses and the subsequent development of DKGF. The determination of this factor as statistically significant in the group of our patients prompted us to improve preventive measures. Our center has developed a device that allowed us the most efficient cooling of the kidney graft from the moment of its immersion in the surgical wound to the moment of reperfusion. We shall evaluate the



efficacy of the device in the prevention of DKGF in further clinical and experimental studies.

*Risk factors that did not reach statistical significance*

A number of factors that did not have a statistically significant relationship to the DKGF development of in our study, may also have an adverse effect on the graft function in the early postoperative period according to the data in world literature. Thus, and absent significant effect of intraoperative blood loss volume on the DKGF development, was associated, in our opinion, with its small mean volume ( $126.5 \pm 72.7$  (95% CI: 117.1–136.0) ml); and the lack of the impact of the donor and recipient HLA mismatches on the DKGF incidence was probably associated with hyperimmunosuppression occurred in 27% of our patients and a small number of cases.

**Multivariate analysis.** In the multivariate model, two factors reached statistical significance: an increased donor BMI (over  $30 \text{ kg/m}^2$ ) ( $p=0.025$ ) and the highest zero concentration of tacrolimus in the first 4 days (more than  $23 \text{ ng/mL}$ ) ( $p=0.017$ ). Patients with oligoanuria (urine less than  $250 \text{ ml/day}$ ) before transplantation were 2.3 times more likely to develop DKGF than candidates with preserved diuresis, but only with a trend towards statistical significance ( $p=0.066$ ). A similar trend was demonstrated by an increase in the graft arterial blood flow resistance index of more than 0.75 after surgery ( $p=0.056$ ). It would not be entirely correct to refer the increased resistance index to risk factors for DKGF, it is rather a useful predictor of its development, sensitive and specific in determining the severity of ischemia-reperfusion preservation graft injury (IRI). At the same time, there are probably additional reasons that increase the IRI, which are currently unknown.

*Donor BMI over 30 kg/m<sup>2</sup>.* A high donor BMI is an independent and, unfortunately, non-modifiable risk factor. The use of overweight donors is one of the options for expanding the criteria for donation, which makes it possible to obtain several times more organs for transplantation to needy patients. Meanwhile, the Implementation of perfusion technologies to replace static cold preservation to replace a static cold preservation for the kidneys from expanded criteria donors is likely to reduce the significance of the donor component in the DKGF development.

*The highest zero concentration of tacrolimus is more than 23 ng/mL in the first 4 days.* The identification of this risk factor for the DKGF development as an independent and modifiable one aroused the greatest interest among the co-authors of this study. The nephrotoxicity of calcineurin inhibitors is a well-known effect of this group of drugs, but only a few authors indicate its significance in the etiological structure of DKGF [28, 29]. Minimization of immunosuppressive therapy in order to reduce its side effects is a current global trend. For example, the London Health Science Center protocol for immunosuppression in the early postoperative period after KT from a standard criteria donor (<https://www.lhsc.on.ca/media/9684/download>) recommends a three-component regimen with a starting dose of extended-release tacrolimus 0.15 mg/kg. According to London authors, the target concentration of tacrolimus in the first 3 months should be  $6.5 \pm 0.5$  ng/mL for patients with a low immunological risk and  $7.0 \pm 0.5$  ng/mL for patients with a high one. For comparison, the tacrolimus concentration in the three –component regimen with mycophenolates and steroids, according to the National Clinical Guidelines for Kidney Transplantation (2020), should be in the range of 8-15 ng/mL within 1 month after surgery and 8-12 ng/mL in the following 2-3 months. The starting dose of tacrolimus on the first day

after surgery is recommended in the range of 0.1–0.2 mg/kg in two doses (depending on the initial graft function). This is probably due to the increased alertness of the nephrotransplantation community to the development of rejection. Unfortunately, some immunosuppressive drugs for the prevention and treatment of acute rejection are either not registered or have limited availability and high cost, and therefore minimizing immunosuppression may be associated with an unacceptable risk of a steroid-resistant rejection and graft loss. At the same time, when working according to the protocol existing in the clinic, we saw that more than half of our patients had a tacrolimus concentration of more than 20 ng/mL in the first days after surgery and, accordingly, higher risks of its toxic effect.

In the course of an additional analysis of the impact of an increased tacrolimus concentration on the development of other early postoperative complications, in addition to DKGF, we revealed its statistically significant relationship with an increase in the incidence of infectious complications. This clearly confirmed the need to revise the traditional protocol and improve the approach to prescribing tacrolimus with lowering the starting dose.

Our study once again confirmed a high prevalence of the delayed graft function (24.5%) of a kidney from a post-mortem donor and its adverse effect on long-term graft survival. In a univariate analysis, we identified 9 statistically significant factors, at least 3 of which were potentially modifiable. In the multivariate model, an elevated tacrolimus concentration was the most significant modifiable risk factor, which prompted the authors to reconsider the existing immunosuppressive protocol at the center.

Thus, given the large number of risk factors for DKGF development differently manifested depending on the country, region, the

level of donation development, and the experience of transplant experts, we consider it an important task for each kidney transplant center to search for modifiable statistically significant risk factors for their patients, their analysis and implementation of preventive measures.

**Limitations.** The main limitations of our study, first of all, include its retrospective nature, the use of data from a single center, a small number of patients, and short follow-up periods. Also, some known risk factors for DKGF have not been analyzed yet in our work. The categorization of quantitative variables for which a statistically significant relationship with a grouping trait was found, which was used in our work, unfortunately leads to a decrease in the prognostic significance of the factor. However, its implementation allowed us to calculate the OR and more clearly demonstrate our results.

## **Conclusions**

1. The incidence of delayed kidney graft function in kidney transplantation from a post-mortem donor reaches 24.5%, and its increase is statistically significantly associated with an increased body weight of the donor and/or recipient, male gender, oligoanuria, and the presence of pre-transplant anti-HLA antibodies in the recipient, and also a number of perioperative parameters, including prolonged time of the operation and second warm ischemia, increased arterial blood flow resistance index in the graft when measured intraoperatively, and acute nephrotoxicity of calcineurin inhibitors.

2. The presence of delayed kidney graft function in our patients was statistically significantly associated with the development of severe postoperative complications and a decrease in long-term survival of kidney grafts ( $p < 0.05$ ), which dictates the need to develop and implement additional measures to prevent its modifiable risk factors.

## References

1. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, et al. KDIGO Clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation*. 2020;104(4Suppl 1):S11–S103. PMID: 32301874 <https://doi.org/10.1097/TP.00000000000003136>
2. Al Otaibi T, Ahmadpoor P, Allawi AA, Habhab WT, Khatami MR, Nafar M, et al. Delayed graft function in living-donor kidney transplant: a middle eastern perspective. *Exp Clin Transplant*. 2016;14(1):1–11. PMID: 26862818.
3. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Schnitzler MA, et al. OPTN/SRTR 2012 Annual data report: kidney. *Am J Transplant*. 2014;14(Suppl 1):11–44. PMID: 24373166 <https://doi.org/10.1111/ajt.12579>
4. Shaheen FA, Attar B, Hejaili F, Binsalih S, Al Sayyari A. Comparison of expanded criteria kidneys with 2-tier standard criteria kidneys: role of delayed graft function in short-term graft outcome. *Exp Clin Transplant*. 2012;10(1):18–23. PMID: 22309415 <https://doi.org/10.6002/ect.2011.0147>
5. Mannon RB. delayed graft function: the AKI of kidney transplantation. *Nephron*. 2018;140(2):94–98. PMID: 30007955 <https://doi.org/10.1159/000491558>
6. Bahl D, Haddad Z, Dattoo A, Qazi YA. Delayed graft function in kidney transplantation. *Curr Opin Organ Transplant*. 2019;24(1):82–86. PMID: 30540574 <https://doi.org/10.1097/MOT.0000000000000604.b>
7. Shabunin AV, Parfenov IP, Minina MG, Drozdov PA, Nesterenko IV, Makeev DA, et al. Botkin Hospital Transplant Program: 100 solid organ transplantations. *Russian Journal of Transplantology and*

*Artificial Organs.* 2020;22(1):55–58. (In Russ.).  
<https://doi.org/10.15825/1995-1191-2020-1-55-58>

8. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant.* 2011;11(11):2279–2296. PMID: 21929642 <https://doi.org/10.1111/j.1600-6143.2011.03754.x>

9. Narayanan R, Cardella CJ, Cattran DC, Cole EH, Tinckam KJ, Schiff J, et al. Delayed graft function and the risk of death with graft function in living donor kidney transplant recipients. *Am J Kidney Dis.* 2010;56(5):961–970. PMID: 20870331  
<https://doi.org/10.1053/j.ajkd.2010.06.024>

10. Tapiawala SN, Tinckam KJ, Cardella CJ, Schiff J, Cattranet DC, Cole EH, et al. Delayed graft function and the risk for death with a functioning graft. *J Am Soc Nephrology.* 2010;21(1):153–161. PMID: 19875806 <https://doi.org/10.1681/ASN.2009040412>

11. Nagaraja P, Roberts GW, Stephens M, Horvath S, Fialovaet J, Chavez R, et al. Influence of delayed graft function and acute rejection on outcomes after kidney transplantation from donors after cardiac death. *Transplantation.* 2012;94(12):1218–1223. PMID: 23154212  
<https://doi.org/10.1097/TP.0b013e3182708e30>

12. Kayler LK, Magliocca J, Zendejas I, Srinivas TR, Schold JD. Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis. *Am J Transplant.* 2011;11(12):2647–2656. PMID: 21906257 <https://doi.org/10.1111/j.1600-6143.2011.03741.x>

13. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. *Kidney Int.* 2015;88(4):851–858. PMID: 26108067  
<https://doi.org/10.1038/ki.2015.190>

14. Yarlagadda SG, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2009;24(3):1039–1047. PMID: 19103734 <https://doi.org/10.1093/ndt/gfn667>

15. Maanaoui M, Provôt F, Bouyé S, Lionet A, Lenain R, Fages V, et al. Impaired renal function before kidney procurement has a deleterious impact on allograft survival in very old deceased kidney donors. *Sci Rep*. 2021;11(1):12226. PMID: 34108573 <https://doi.org/10.1038/s41598-021-91843-7>

16. Kim KD, Lee KW, Kim SJ, Lee O, Lim M, Jeong ES, et al. Safety and effectiveness of kidney transplantation using a donation after brain death donor with acute kidney injury: a retrospective cohort study. *Sci Rep*. 2021;11(1):5572. PMID: 33692385 <https://doi.org/10.1038/s41598-021-84977-1>

17. Cha SW, Shin, IS, Kim DG, Kim SH, Lee JY, Kim SJ, et al. Effectiveness of serum beta-2 microglobulin as a tool for evaluating donor kidney status for transplantation. *Sci Rep*. 2020;10(1):8109. PMID: 32415140 <https://doi.org/10.1038/s41598-020-65134-6>

18. Melih KV, Boynuegri B, Mustafa C, Nilgun A. Incidence, risk factors, and outcomes of delayed graft function in deceased donor kidney transplantation. *Transplant Proc*. 2019;51(4):1096–1100. PMID: 31101179 <https://doi.org/10.1016/j.transproceed.2019.02.013>

19. Jahn L, Rüster C, Schlosser M, Winkler Y, Foller S, Grimm M-O, et al. Rate, factors, and outcome of delayed graft function after kidney transplantation of deceased donors. *Transplant Proc*.

2021;53(5):1454–1461. PMID: 33612277

<https://doi.org/10.1016/j.transproceed.2021.01.006>

20. Kernig K, Albrecht V, Dräger DL, Führer A, Mitzner S, Kundt G, et al. Predictors of delayed graft function in renal transplantation. *Urol Int.* 2022;106(5):512–517. PMID: 34915519

<https://doi.org/10.1159/000520055>

21. Tagoev SKh, Gulov MK, Sharipova KhYo, Alimova NA. Clinical and hemodynamic factors affecting the initial function of renal allograft. *Avicenna Bulletin.* 2019;21(2):279-84. (In Russ.).

<https://doi.org/10.25005/2074-0581-2019-21-2-279-284>

22. Redfield RR, Scalea JR, Zens TJ, Muth B, Kaufman DB, Djamali A, et al. Predictors and outcomes of delayed graft function after living-donor kidney transplantation. *Transpl Int.* 2016;29(1):81–7. PMID: 26432507 <https://doi.org/10.1111/tri.12696>

23. Pan J, Liao G. Development and validation of nomogram for predicting delayed graft function after kidney transplantation of deceased donor. *Int J Gen Med.* 2021;14:9103–9115 PMID: 34876844 <https://doi.org/10.2147/IJGM.S331854>

24. Gorayeb-Polacchini FS, Caldas HC, Fernandes-Charpiot IMM, Ferreira-Baptista MAS, Gauch CR, Abbud-Filho M. Impact of cold ischemia time on kidney transplant: a meta kidney analysis. *Transpl Proc.* 2020;52(5):1269–1271. PMID: 32204899

<https://doi.org/10.1016/j.transproceed.2019.12.052>

25. Serrano OK, Vock DM, Chinnakotla S, Dunn TB, Kandaswamy R, Pruett TL, et al. The relationships between cold ischemia time, kidney transplant length of stay, and transplant-related costs. *Transplantation.* 2019;103(2):401–411. PMID: 29863580

<https://doi.org/10.1097/TP.0000000000002309>



26. Lauronen J, Peräsaari JP, Saarinen T, Jaatinen T, Lempinen M, Helanterä I. Shorter cold ischemia time in deceased donor kidney transplantation reduces the incidence of delayed graft function especially among highly sensitized patients and kidneys from older donors. *Transpl Proc.* 2020;52(1):42–49. PMID: 31901321 <https://doi.org/10.1016/j.transproceed.2019.11.025>

27. Brennan C, Sandoval PR, Husain SA, King KL, Dube GK, Tsapepas D, et al. Impact of warm ischemia time on outcomes for kidneys donated after cardiac death Post-KAS. *Clin Transplant.* 2020;34(9):e14040. PMID: 32654278 <https://doi.org/10.1111/ctr.14040>

28. Shabunin AV, Minina MG, Drozdov PA, Nesterenko IV, Makeev DA, Zhuravel OS. First results of hypothermic oxygenated renal transplant perfusion. *Russian Journal of Transplantology and Artificial Organs.* 2021;23(S):109. (In Russ.).

29. Kamińska D, Kościelska-Kasprzak K, Chudoba P, Hałoń A, Mazanowska O, Gomółkiewicz A, et al. The influence of warm ischemia elimination on kidney injury during transplantation – clinical and molecular study. *Sci Rep.* 2016;6(1):1-10. PMID: 27808277 <https://doi.org/10.1038/srep36118>

30. Liu Y, Liu H, Shen Y, Chen Y, Cheng Y. Delayed initiation of tacrolimus is safe and effective in renal transplant recipients with delayed and slow graft function. *Transpl Proc.* 2018;50(8):2368–2370. PMID: 30316359 <https://doi.org/10.1016/j.transproceed.2018.0>

31. Gonwa TA, Mai ML, Smith LB, Levy MF, Goldstein RM, Klintmalm GB. Immunosuppression for delayed or slow graft function in primary cadave-ric renal transplantation: use of low dose tacrolimus therapy with post-operative administration of anti-CD25 monoclonal

antibody. *Clin Transplant*. 2002;16(2):144–149. PMID: 11966785  
<https://doi.org/10.1034/j.1399-0012.2002.1o078.x>

32. Stallone G, Pontrelli P, Rascio F, Castellano G, Gesualdo L, Grandaliano G. Coagulation and fibrinolysis in kidney graft rejection. *Front Immunol*. 2020;11:1807. PMID: 32983089  
<https://doi.org/10.3389/fimmu.2020.01807>

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