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Relevance of KDPI value and acute rejection on kidney transplant outcomes in recipients with delayed graft function – a retrospective study

Carlos E. Arias-Cabrales[1]*, María José Pérez-Sáez[1]*, Dolores Redondo-Pachón[1], Anna Buxeda[1], Carla Burballa[1], Xavier Duran[2], Marisa Mir[1], Marta Crespo[1] & Julio Pascual[1]

1 Nephrology, Hospital del Mar, Barcelona, Spain
2 Methodological and Biostatistics consultancy, Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain

Correspondence
Julio Pascual, Nephrology, Hospital del Mar, passeig maritim 35-39, 08003 Barcelona, Spain.
Tel: 932 48 30 00;
fax: +34 932 483 373;
email: julpascual@gmail.com

*Contributed equally.

SUMMARY

Delayed graft function (DGF) is associated with poorer graft survival and higher rate of acute rejection (AR). It is unknown whether this negative influence relies on the increased risk of AR or the DGF itself. The different Kidney Donor Profile Index (KDPI) values may also play a role in this interaction. Retrospective study aimed to evaluate the impact of DGF on graft function and graft survival in a subset of KT recipients (2004–2017). We also analyzed the relationship between KDPI and DGF. The study includes 601 KT, 226 of them (37%) developed DGF. Graft survival was lower in patients with DGF compared with non-DGF patients. Multivariable analysis revealed DGF as risk factor for graft loss, independently of the presence or not of acute rejection. Between DGF patients, we observed poorer graft survival in patients with higher KDPI value (>85%). We observed a trend of a greater impact of KDPI in patients with DGF, although this interaction was not statistically significant. Additionally, we observed poorer 12-month graft function in DGF patients. DGF is related to poorer graft survival independently of the developed acute rejection. This negative impact might be influenced by high KDPI values.

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Introduction

Delayed graft function (DGF) is a frequent complication after kidney transplantation (KT), most frequently defined as the need for dialysis during the first week after transplantation [1]. Although important advances regarding immunosuppression and organ allocation strategies have led to reduce the incidence of DGF, it still remains significant, meaning 20–50% of deceased-donor KT recipients [2]. This may be related to the expansion in donor/recipient acceptance criteria and the increase in the utilization of kidneys from donor after circulatory death [3,4]. However, this incidence can be very variable due to heterogeneous definitions [1] and transplant center effect [5].

The ischemia/reperfusion damage is postulated as one of the principal causes of DGF, with mechanisms that include immunological and nonimmunological events [6,7].

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In this line, several studies reported a relationship between DGF and acute rejection (AR)[8,9]. Whether the negative impact of DGF on graft outcomes might be explained by the underlying acute rejection or by isolated ischemia/reperfusion damage is not clear. Some studies reported shorter allograft survival regardless of rejection occurrence [10–12], while these results are not homogeneous [13,14].

On the other hand, little is known about the impact of DGF on graft survival depending on the Kidney Donor Profile Index (KDPI) value, and their potential interaction. To date, only one study performed in US population evaluated the relationship between KDPI and DGF, showed higher DGF rates and lower graft and patient survival with increasing KDPI [15].

However, most of the above-mentioned studies were developed in different KT era and with different allocation policies. This potential interaction should be analyzed in modern cohorts with current immunosuppression treatments and with more expansive policies for donor and recipient selection.

Our main aim was to evaluate the impact DGF on graft survival and 12-month graft function. In addition, we evaluated whether the potential DGF impact on graft outcomes might be related to the presence or not of acute rejection, and the interaction between KDPI and DGF as predictor tools for graft outcomes.

Patients and methods

Study design and data collection

Retrospective study with an initial cohort of 720 deceased-donor KT recipients performed in our center between January 2004 and December 2017. We excluded KT from donors younger than 18 years old ($n = 11$), living donor KT ($n = 29$), cases of early graft lost due to arterial or venous thrombosis ($n = 11$), and recipient death during the first week after KT ($n = 3$), and all cases with missing data necessary to calculate KDPI score ($n = 65$). Finally, 601 transplants performed in 570 patients were analyzed. Median time of follow-up was 34.8 months [interquartile range (IQR), 14.9–74.4].

Clinical data were collected from our local transplant database, which includes: baseline demographic characteristics from donors and recipients, transplant characteristics and clinical follow-up variables periodically registered, complications and patient/graft survival. The study was undertaken following the principles of the declaration of Helsinki, only relying in the official center database.

Definitions

DGF was defined as dialysis needed during the first week after transplantation. KDPI was calculated from donor variables including age, race, diabetes, hypertension, serum creatinine, height, weight, hepatitis C seropositivity, and cause of death, using the method described by the Organ Procurement Transplant Network [16]. This KDPI value was calculated during 2018, using 2017 KDPI reference values.

Outcomes

We evaluated graft failure (defined as the need for renal replacement therapy, preemptive retransplantation, or death with functioning graft), death-censored graft failure, and 12-month graft function (defined by serum creatinine).

Statistical analysis

Descriptive statistics according to the nature of the variables and presented in tables have been used to describe the patient data. The nominal categorical variables have been described by means of the number of cases and the percentage with respect to the total by category. Continuous variables have been described using the mean and standard deviation or the median, the first and third quartiles.

Survival analyses have been performed with graft failure and death-censored graft failure as an event. For this, Kaplan–Meier curves have been performed, first differentiating by DGF and then by DGF and KDPI ≥ 85. In addition, Cox models have been carried out in which the possible interaction between both variables has been taken into account. Independent models with donor age instead of KDPI and with recipient age instead KDPI or donor age were performed by convergence problems. Baseline data have been included as predictors, except recipient age due to strong collinearity with relevant predictors as donor age and KDPI.

Finally, creatinine was studied at 12 months, using a multiple linear regression applied to the logarithm of creatinine values. Baseline data have been included as regressors.

Statistical analysis was performed using SPSS V 25.0 (SPSS Inc., Chicago, IL, USA) and with software R 3.6.3

Results

From a total of 601 KT recipients, 37% presented with DGF. Donors were more frequently male (65.9 vs. 55.8

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%) and older (57.6 ± 13.9 vs. 54.5 ± 16 years) in the DGF group. DGF recipients had more frequently arterial hypertension (91.1 vs. 75.2%) and with hemodialysis as RRT modality (100 vs. 95.5%). Time on dialysis prior KT was longer in DGF recipients (24 [IQR = 15–42.0] vs. 20 [IQR = 11–32] months). We found similar values of KDPI between DGF and non-DGF patients, with almost the same proportion of patients with high KDPI value (>85%) in both groups (Table 1).

Ninety-nine grafts were lost during the follow-up (median time 3 years). DGF patients had higher rates of death-censored graft loss (13.3 vs. 6.4%; $P = 0.005$, Table 2) and also patient mortality was higher (10.6 vs. 5.6; $P = 0.035$, Table 2).

Kaplan–Meier survival analysis showed lower graft survival and death-censored graft survival among KT recipients with DGF (Fig. 1).

DGF was an independent risk factor for graft failure (HR 1.75 95% CI 1.14 to 2.68, $P = 0.010$) and death-censored graft failure (HR 1.96 95% CI 1.10 to 3.50, $P = 0.023$) in the multivariable Cox regression analysis (Table 3). After excluding patients who suffered from acute rejection, DGF was still a risk factor for both outcomes (Table 3).

The Kaplan–Meier survival analysis of patients groups based on KDPI values (> or < 85%) and the presence/no of DGF showed the lowest graft survival in the group of DGF and KDPI > 85%, without differences between the others groups (non-DGF + KDPI<85%, non-DGF + KDPI>85%, and DGF + KDPI<85%) (Fig. 2). Despite we found a tendency to higher rates of graft failure and death-censored graft failure between those patients with DGF and high KDPI, the interaction between KDPI or KDPI> 85% and DGF was not statistically significant in multivariable Cox models (Table 3).

Regarding 1-year renal function, serum creatinine was higher in DGF group (1.57 ± 0.65 vs. 1.80 ± 0.70 mg/dl, $P = 0.004$). The multiple linear regression showed that DGF was related to worse12-month graft function (Table 4).

Discussion

In this study, we showed that DGF has an impact on KT outcomes, lowering 1-year graft function and graft survival despite the presence or not of acute rejection. However, if we consider donors with KDPI values < 85%, DGF did not present with poorer graft survival, although no clear interaction between DGF and KDPI was confirmed in multivariable survival analysis.

The incidence of DGF ranges from 20% to 50% in deceased-donor KT recipients [3,8,9,17], depending on

Table 1. Baseline characteristics of DGF and non-DGF patients

	Non-DGF *n* = 375	DGF *n* = 226
Donor age, mean (standard deviation)	54.5 (16.0)	57.6 (13.9)
Donor sex (male), *n* (%):	208 (55.8%)	149 (65.9%)
KDPI, median [Q1-Q3]	78.0 [48–94]	80.0 [57–96]
KDPI ≥ 85, *n* (%):	141 (41.8%)	83 (41.1%)
Recipient age, mean (standard deviation)	54.5 (13.6)	58.0 (12.3)
Recipient sex (male), *n* (%):	243 (64.8%)	153 (67.7%)
Recipient arterial hypertension, *n* (%):	282 (75.2%)	205 (91.1%)
Recipient diabetes mellitus, *n* (%):	55 (14.9%)	32 (14.5%)
Recipient cardiac disease, *n* (%):	194 (51.7%)	133 (58.8%)
Pretransplant hemodialysis, *n* (%):	240 (95.6%)	177 (100%)
Months on dialysis prior to KT, median [Q1–Q3]	20.0 [11–32]	24.0 [15–42]
Previous KT, *n* (%):	45 (14.1%)	38 (19.8%)
Peak PRA> 30%, *n* (%):	18 (5.73%)	16 (8.25%)
Cold ischemia time (hours), median [Q1–Q3]	14 [10–17]	15 [12–20]
Donor after circulatory death, *n* (%)	35 (9.3%)	42 (18.5%)
Induction immunosuppression, *n* (%):		
Noninduction	14 (3.73%)	4 (1.77%)
Anti-CD 25	299 (79.7%)	169 (74.8%)
Thymoglobulin	62 (16.5%)	53 (23.5%)
Days to creatinine decrease, median [Q1–Q3]	3 [1–5]	11 [7–16]
Follow-up (months), median [Q1–Q3]	31 [13–70]	37.4 [15–88]

DGF, delayed graft function; KDPI, kidney donor profile index; KT, kidney transplant; PRA, panel reactive antibody

Table 2. Incidence of events among DGF and non-DGF patients

	Non-DGF *n* = 375	DGF *n* = 226	*P*-value
Acute rejection, *n* (%)			0.100
No	341 (90.9)	195 (86.3)	
Yes	24 (9.07)	31 (13.7)	
Mortality, *n* (%)			0.035
No	354 (94.4%)	202 (89.4%)	
Yes	21 (5.60%)	24 (10.6%)	
Death-censored graft failure, n (%)			0.005
No	349 (93.6%)	195 (86.7%)	
Yes	24 (6.43%)	30 (13.3%)	
12-month creatinine, median (SD)	1.57 (0.65)	1.80 (0.70)	0.004

DGF, delayed graft function; SD, standard deviation

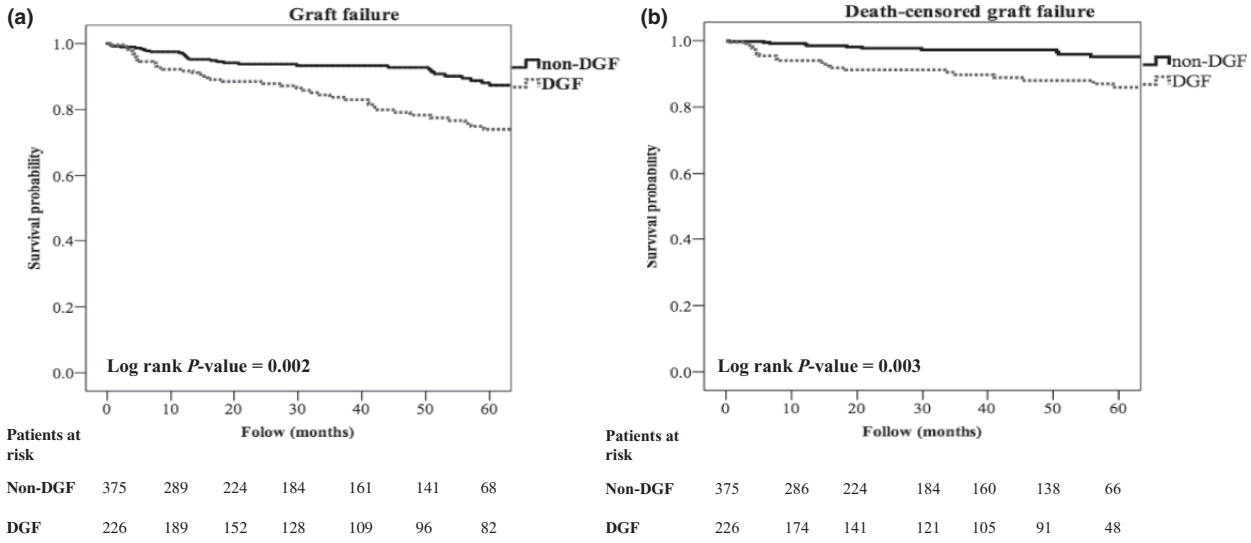

Figure 1 Kaplan–Meier plots showing graft failure and death-censored graft failure.

recipient, donor, and transplant factors, as well as DGF definition used[1,18]. In our cohort, 37% of patients had DGF, considering DGF as dialysis needed during the first seven days after KT.

Several studies have reported a relationship between DGF and higher risk of graft failure. In a meta-analysis with 33 studies and 151 594 KT recipients, DGF associated with 41% increase risk of graft loss and higher serum creatinine at 3.5 years of follow-up [8]. Our patients with DGF presented with 1.5- to 2-fold higher risk of graft loss and death-censored graft loss.

Some studies postulated that this poorer survival could be explained by the increased incidence of acute rejection in patients suffering from DGF [9,13,14]. However, other authors have demonstrated that DGF has a negative impact even in the absence of acute rejection [10–12]. In the meta-analysis mentioned before, the authors performed a subgroup analysis with five studies in which acute rejection was clearly differentiated from DGF as a cause of graft dysfunction. The risk of graft loss in these studies was very similar of the overall point estimate from the meta-analysis [8]. In this line, we have not found a higher rate of acute rejection among DGF patients compared with non-DGF patients (13% vs. 9.0%, $P = 0.100$). We neither found relevant changes in the results of the multivariable Cox models when evaluating graft failure and death-censored graft failure if we

Table 3. Multivariable Cox analysis of graft loss and death-censored graft loss

	Graft Loss		Death-censored graft loss	
Predictors	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value
DGF	1.75 (1.14 to 2.68)	0.010	1.96 (1.10 to 3.50)	0.023
KDPI	2.03 (1.54 to 2.69)	<0.001	1.57 (1.06 to 2.11)	0.020
KDPI> 85%	1.66 (0.80 to 3.48)	0.172	1.15 (0.43 to 3.07)	0.783
Donor sex (female)	1.66 (1.08 to 2.54)	0.025	2.0 (1.06 to 3.75)	0.031
Donor age*	2.05 (1.60 to 2.63)	<0.001	1.50 (1.06 to 2.11)	0.020
Months on dialysis prior to KT	1.00 (1.00 to 1.01)	0.285	1.01 (1.01 to 1.02)	0.035
Recipient age†	1.78 (1.26 to 2.52)	0.001	1.35 (0.97 to 1.87)	0.076
Recipient arterial hypertension	1.55 (0.75 to 3.19)	0.234	1.04 (0.42 to 2.63)	0.927
Recipient diabetes mellitus	1.31 (0.77 to 2.21)	0.316	2.25 (1.09 to 4.64)	0.027
Recipient peripheral vascular disease	1.90 (1.04 to 3.47)	0.036	0.58 (0.22 to 1.56)	0.282
DCD vs DBD donor	1.52 (0.70 to 3.30)	0.280	1.03 (0.48 to 2.23)	0.926
DGF-KDPI interaction	1.05 (0.63 to 1.77)	0.851	1.56 (0.76 to 3.21)	0.228
DGF-KDPI> 85% Interaction	1.01 (0.57 to 1.80)	0.973	1.59 (0.48 to 5.29)	0.446
DGF without AR‡	1.69 (1.05 to 2.70)	0.030	1.85 (1.08 to 3.68)	0.010

DGF, delayed graft function; KT, kidney transplant; DCD, donor after circulatory death; DBD, donor after brain death; AR acute rejection

*Data from an independent model with donor age instead of KDPI and all the others predictors

†Data from an independent model with recipient age instead of KDPI and all the others predictors

‡Data from an independent model with the same predictors excluding patients with any episode of acute rejection

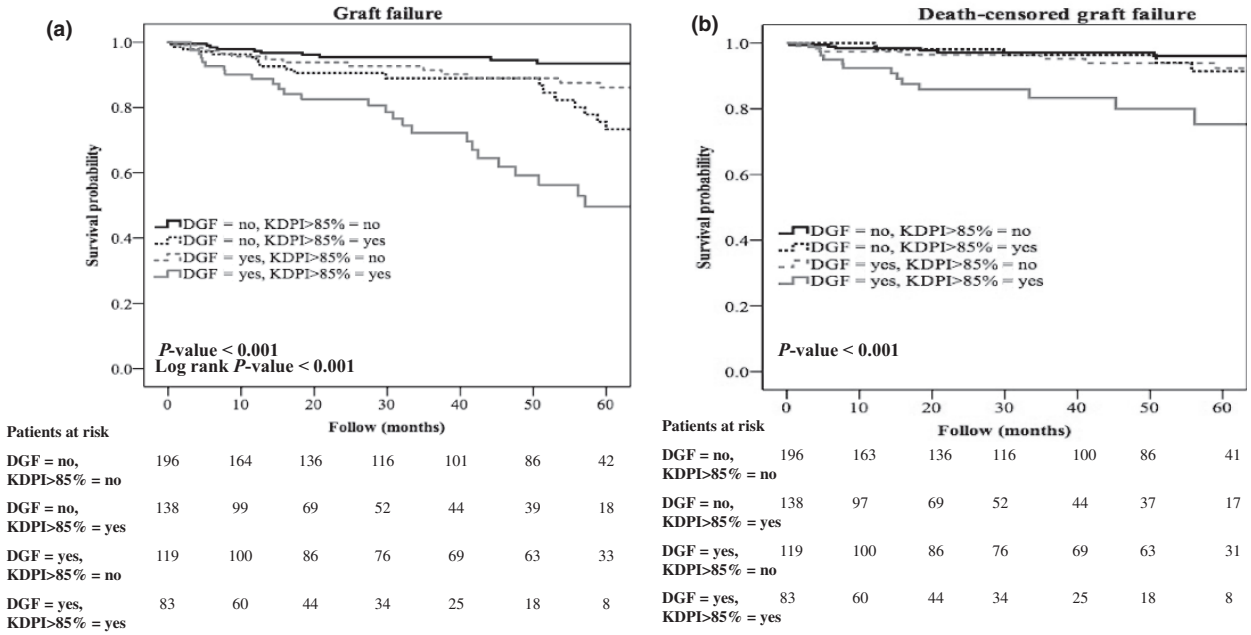

Figure 2 Kaplan–Meier plots showing graft failure and death-censored graft failure in non-DGF patients compared with DGF patients and different KDPI value.

included or not patients with acute rejection. In all the analysis performed, DGF was still as risk factor to both outcomes.

The risk of graft failure in our study was higher compared with other studies [8]. This difference might be explaining by the differences between most of the

Table 4. Independent risk factors for 12-month serum creatinine

Predictor	B-Coefficient	Min	Max	*P*-value
DGF	0.12	0.06	0.18	<0.001
KDPI	0.01	0.00	0.05	0.695
Donor age	0.01	0.00	0.01	<0.001
Recipient DM	0.14	0.05	0.22	0.001
Recipient age	0.00	−0.00	0.01	0.262
Previous KT	0.00	−0.10	0.10	0.959
PRA> 30%	0.07	0.13	0.27	0.479
IS induction (Thymoglobulin)	−0.02	−0.19	0.15	0.815

DGF, delayed graft function; KDPI, kidney donor profile index; DM, diabetes mellitus; KT, kidney transplant; PRA, panel reactive antibody; IS immunosuppression

cohorts included in previous studies and our cohort, with older donors and, consequently, poorer outcomes. In this line, one of the aims of our study was to evaluate the influence of donor characteristics reflected in KDPI score on graft outcome between DGF patients. Although the KDPI value was similar between DGF and not DGF patients, we detected a relationship between the combination of higher KDPI values plus DGF with lower graft survival, and patients with DGF but lower KDPI values presented with similar survival than patients without DGF. Unfortunately, this interaction was not confirmed in the multivariable analysis, probably related to the poorer statistical power due to the low number of events. However, it seems that the risk effect of KDPI would be greater in patients with DGF and less relevant in patients without DGF. Few studies have analyzed this interaction between DGF and KDPI. To our knowledge, this is the first study that evaluated the interaction between KDPI values and DGF regarding graft survival in a European population.

Graft function was also poorer in DGF patients, even after multivariable robust regression analysis. These results seem to be more related to donor and recipient characteristics (as donor age and history of recipient history of diabetes mellitus) than immunological factors as higher pretransplant PRA value. Other studies have also reported a negative impact of DGF on graft function [19–22].

Our analysis has some limitations. First, as a result of its retrospective nature, a number of cases had to be excluded due to missing crucial data to calculate the prognostic scores. Loss of data was due to arbitrary failure in the manual entry of information in the transplant records. We consider that the exclusion of the patients with missing scoring values was not associated with any recipient or donor characteristics and thus should not bias our results. Secondly, Caucasian donors and recipients compose the vast majority of our sample. Therefore, our results cannot be extrapolated to subjects of other ethnic groups. In addition, even with an appreciable sample size, the low number of graft losses could reduce the statistical power of the multivariable survival analysis.

But the present study has several strengths too. To our knowledge, this is the first study that offers information regarding the relationship of KDPI and DGF in European population. In addition, this study reported results from an appreciable sample size with long-term follow-up.

In conclusion, DGF has a negative impact on graft survival and one-year graft function even in the absence of clinical AR. Although we cannot confirm statically the interaction between the KDPI value and graft survival among those recipients who developed DGF, we detected a trend that would indicate higher negative impact of DGF in graft from donor with high KDPI values.

Therefore, it is relevant to develop strategies aiming to reduce rates of DGF especially in KT from high KDPI value donors.

Authorship

CA-C MJP-S and JP designed the study, performed the analysis, and validated the data. XD contributed in the data analyses. CA-C and MJP-S drafted the initial report, while all authors contributed to the final manuscript and approved it. CA-C and MJP-S contributed equally.

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Conflicts of interest

The authors have declared no conflicts of interest.

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REFERENCES

1. Yarlagadda SG, Coca SG, Garg AX, *et al*. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. *Nephrol Dial Transplant* 2008; **23**: 2995.
2. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. *Am J Transplant.* 2010; **10**: 2279.
3. Portolés JM, Pérez-Sáez MJ, López-Sánchez P, *et al*. Trasplante renal con órganos procedentes de donación tras parada circulatoria controlada: resultados del estudio multicéntrico GEODAS-3. *Nefrología.* 2019; **39**: 151.
4. On behalf of the GEODAS Group, Pérez-SáezM J, Lafuente Covarrubias O, *et al*. Early outcomes of kidney transplantation from elderly donors after circulatory death (GEODAS study). *BMC Nephrol* 2019;**20**:233.
5. Akkina SK, Connaire JJ, Israni AK, Snyder JJ, Matas AJ, Kasiske BL. Similar outcomes with different rates of delayed graft function may reflect center practice, not center performance. *Am J Transplant* 2009; **9**: 1460.
6. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant: delayed graft function in the kidney transplant. *Am J Transplant* 2011; **11**: 2279.
7. Eltzschig HK, Eckle T. Ischemia and reperfusion—from mechanism to translation. *Nat Med* 2011; **17**: 1391.
8. 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* 2008; **24**: 1039.
9. 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**: 851.
10. Moreso F. Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. *Nephrol Dial Transplant* 1999; **14**: 930.
11. Feldman HI, Gayner R, Berlin JA, *et al*. Delayed function reduces renal allograft survival independent of acute rejection. *Nephrol Dial Transplant* 1996; **11**: 1306.
12. Shoskes DA, Cecka JM. Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection1,2,3. *Transplantation* 1998; **66**: 1697.
13. Troppmann C, Gillingham KJ, Benedetti E, *et al*. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. *Transplantation* 1995; **59**: 962.
14. Mikhalski D, Wissing KM, Ghisdal L, *et al*. ischemia is a major determinant of acute rejection and renal graft survival in the modern era of immunosuppression. *Transplantation* 2008; **85**(Supplement): S3.
15. Zens TJ, Danobeitia JS, Leverson G, *et al*. The impact of kidney donor profile index on delayed graft function and transplant outcomes: A single-center analysis. *Clin Transplant* 2018; **32**: e13190.
16. A Guide to Calculating and Interpreting the Kidney Donor Profle Index (KDPI). Available from: https://optn.transplant.hrsa.gov/resources/guidance/kidney-donor-profile-index-kdpi-guide-for-clinicians/
17. Fernández-Juarez G, Marcén R, Pascual J, *et al*. Prolonged delayed graft function decreases graft survival in transplant patients taking cyclosporine. *Transplant Proc* 2002; **34**: 338.
18. Pérez-Sáez MJ, Montero N, Redondo-Pachón D, Crespo M, Pascual J. Strategies for an expanded use of kidneys from elderly donors. *Transplantation* 2017; **101**: 727.
19. Boom H, Mallat MJK, De Fijter JW, Zwinderman AH, Paul LC. Delayed graft function influences renal function, but not survival. *Kidney Int* 2000; **58**: 859.
20. Wang CJ, Tuffaha A, Phadnis MA, Mahnken JD, Wetmore JB. Association of slow graft function with long-term outcomes in kidney transplant recipients. *Ann Transplant* 2018; **23**: 224.
21. Johnston O, O'Kelly P, Spencer S, *et al*. Reduced graft function (with or without dialysis) vs immediate graft function—a comparison of long-term renal allograft survival. *Nephrol Dial Transplant* 2006; **21**: 2270.
22. Hernández D, Rufino M, González-Posada JM, *et al*. Predicting delayed graft function and mortality in kidney transplantation. *Transplant Rev* 2008; **22**: 21.