ORIGINAL ARTICLE

The impact of functional delayed graft function in the modern era of kidney transplantation – A retrospective study

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ABSTRACT

The dialysis-based definition of Delayed Graft Function (dDGF) is not necessarily objective as it depends on the individual physician's decision. The functional definition of DGF (fDGF, the failure of serum creatinine to decrease by at least 10% daily on 3 consecutive days during the first week post-transplant), may be more sensitive to reflect recovery after the ischemia-reperfusion injury. We retrospectively analyzed both definitions in 253 deceased donor kidney transplant recipients for predicting death-censored graft failure as primary outcome, using eGFR < 25 ml/min/1.73 m^2 as a surrogate end-point for graft failure. Secondary outcome was a composite outcome that included graft failure as above and also patient's death. Median follow-up was 3.22 [2.38–4.21] years. Seventy-nine patients developed dDGF (31.2%) and 127 developed fDGF (50.2%). Sixty-three patients fulfilled criteria for both definitions (24.9%). At multivariable analysis, the two definitions were significantly associated with the primary [HR (95% CI) 2.07 (1.09–3.94), $P = 0.026$ for fDGF and HR (95%CI) 2.41 (1.33–4.37), $P = 0.004$ for dDGF] and the secondary composite outcome [HR (95%CI) 1.58 (1.01–2.51), $P = 0.047$ for fDGF and HR (95%CI) 1.67 (1.05–2.66), $P = 0.028$ for dDGF]. Patients who met criteria for both definitions had the worst prognosis, with a three-year estimates (95%CI) of survival from the primary and secondary outcomes of 2.31 (2.02–2.59) and 2.20 (1.91–2.49) years for fDGF+/dDGF+, in comparison with the other groups ($P < 0.01$ for trend). fDGF provides supplementary information about graft outcomes on top of the dDGF definition in a modern series of kidney transplantation.

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Key words
delayed graft function, dialysis delayed graft function, functional delayed graft function, graft survival, kidney transplantation, recipient survival

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Introduction

Delayed graft function (DGF) is the most important clinical correlate of the ischemia-reperfusion injury after kidney transplantation. Typically, large multicentre studies have relied on the need for postoperative dialysis during the first week after kidney transplant to define DGF [1]. The most significant factors associated with DGF are cold ischemia time (CIT), donor creatinine, body mass index (BMI), donation after cardiac death (DCD) and donor age [2]. Moreover, DGF is an important risk factor for early acute rejection and has been associated with poorer graft survival and short- and long-term renal function, although its impact on patient survival is still controversial [3–5]. In terms of living donor kidney transplantation, DGF is less common, but has also been associated with inferior allograft outcomes [6].

Although simple to recognize, the dialysis-based definition (dDGF) is not entirely objective, as it depends on the physician's subjective evaluation of the necessity for dialysis [7,8]. Moreover, dDGF excludes patients with nonoliguric acute tubular necrosis without need for dialysis who may also have inferior outcomes [7]. On the other hand, it includes patients who require dialysis due to electrolyte alterations (e.g., hyperkalemia or acidosis) that may not necessarily solely reflect glomerular filtration rate (GFR) [7,8]. For this reason, the absence of dDGF does not necessarily imply better allograft outcomes, and long-term graft survival may be shortened even in patients not requiring dialysis [7,9]. Subsequently, a more objective definition of DGF (functional-based, fDGF) was proposed 20 years ago and defined as failure of serum creatinine to decrease by at least 10% daily on three consecutive days during the first week post-transplant [10]. In this first study, fDGF was identified as a risk factor of acute rejection and suboptimal function at one year, but it was not independently associated with an increased rate of graft loss [10]. In 2010, Moore et al [8] reassessed the fDGF definition as a risk factor for long-term graft failure compared to traditional dDGF. In this study, fDGF was independently associated with reduced death-censored graft survival irrespective of dDGF category, and the absence of fDGF portended superior graft survival even in patients requiring postoperative dialysis, suggesting superiority of this new definition over the classical one [8]. Since 2010, the clinical landscape has significantly changed, especially for the increased prevalence of old donors and recipients [11,12] and the differences in immunosuppression (nowadays usually based on tacrolimus, mycophenolate or mTOR inhibitors, [mTORi] rather than cyclosporine and azathioprine) [13,14]. Thus, recently some studies have reassessed the usefulness of alternative DGF definitions which are not exclusively based on dialysis treatment (including that proposed by Boom et. al. [10]), although its superiority to those dialysis-based definitions remains controversial in terms of graft and recipient outcomes [9,15]. Therefore, the purpose of this study was to evaluate the association between fDGF definition and long-term outcomes and also to analyze if it adds some relevant prognostic information especially in those patients who do not fulfill the dialysis-based definition.

Materials and methods

From June 1st 2013 to December 31st 2016, 267 patients received a kidney graft from a deceased donor at the Hospital Clínic of Barcelona, Spain. From the initial population, 12 patients have been excluded for primary nonfunction, and 2 for cyclosporine-based immunosuppression for a final *n* of 253 patients. dDGF definition required at least a dialysis session during the first week after kidney transplant, prescribed according to the criteria of the attending physician. fDGF was defined as the failure of serum creatinine to decrease by at least 10% daily on three consecutive days during the first week after kidney transplant [10]. For patients receiving dialysis after transplantation, we applied the same fDGF definition, without taking into account the decrease in creatinine of the day after the dialysis session. In our center, induction is based on either anti-thymocyte or anti-CD25 antibodies according to the immunological risk, while baseline immunosuppression is based on tacrolimus associated with either mycophenolate or mTOR inhibitors and prednisone, as previously described [16]. The first dose of tacrolimus is administered before transplantation and the management is independent of the development of DGF. As the median follow-up time was relatively short (3.22 [2.38–4.21] years, end of follow-up April 30th 2019), the graft loss rate was reduced as well. Thus, similar to previous studies [9], estimated Glomerular Filtration Rate (eGFR) < 25 ml/min/1.73 m^2 (according to the CKD-EPI equation) was also chosen as a surrogate end-point for graft failure. Therefore, the primary outcome (death-censored graft failure) was defined as freedom from eGFR < 25ml/min/1.73 m^2 (including graft failure), while the secondary outcome was defined as freedom from a composite of eGFR < 25ml/min/1.73 m^2 (including graft failure) or patient's death.

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The relationship of the two definitions of DGF with the primary and secondary outcomes was examined estimating hazard ratios (HR) and their 95% confidence intervals (95%CI) by means of Cox-regression analysis. This was also performed with all the following covariates: recipient age, donor's expanded criteria (ECD) status, donor and recipient sex, previous transplant, immunological risk (expressed as a basal calculated panel-reactive antibodies [cPRA]> 50%), cold ischemia time, type of induction, baseline immunosuppression and biopsy-proven acute rejection (BPAR) developed during the first year after kidney transplantation. In order to study the independent association of fDGF and dDGF with the outcomes, Cox-regression bivariable and multivariable analyses were performed by taking into account all the covariates with P-values ≤ 0.1 at univariable analyses. The association of different combinations of fDGF and dDGF with the primary and the secondary outcomes was assessed as the Kaplan–Meier estimates of survival with 95% CI at 3-year follow-up. A log-rank test was run to analyze if there were differences in the survival distribution among groups.

The impact of different combination of fDGF and dDGF on 1-year renal function expressed as the eGFR and chronicity scores at protocol renal biopsy according to the Banff 2017 criteria [17] was also investigated. This was performed by Analysis of Variance (ANOVA) test with LSD post hoc analysis to explore differences among groups. The association of pretransplant factors with the development of fDGF and dDGF was assessed as OR with 95% CI from univariate logistic regression models.

All statistical tests have been conducted with a 95% confidence interval and a P-value < 0.05 has been considered significant. To carry out all the analyses, the software SPSS v.25 (SPSS inc, Chicago, IL, US) was used. Graphical representation of Kaplan–Meier curve was designed with GraphPad v.5 (GraphPad Software, La Jolla, CA, US). The Hospital Clínic Institutional Ethics Committee approved the study.

Results

Baseline characteristics and outcomes of the studied population

Baseline characteristics of the studied population are displayed in Table 1. A total number of 253 patients were analyzed. Mean age of the recipients was 61.21 ± 10.73 years with the male sex most represented (63.6%). Donor age was 61.70 ± 13.67 years, with male sex predominance (60.5%). Diabetes mellitus was present in 29.2% of patients. In most cases, patients were receiving hemodialysis before transplantation (80.2%), with mean dialysis vintage of 52.51 ± 50.68 months. Immunological risk was low-to-moderate with a cPRA I + II of 15.98 ± 33.45%. Most donors were after brain death (DBD, 61.7%) and induction consisted in basiliximab in 56.5% of cases, while anti-thymocyte globulins were employed in 38.3% of patients. Primary immunosuppression was based on tacrolimus and prednisone associated with either mycophenolate (82 patients, 32.4%) or mTORi (everolimus, or sirolimus, 171 patients, 67.6%) (Table 1).

Table 1. Baseline characteristics of the studied population

	Total population (n = 253)
Recipient age (years)	61.21 ± 10.73
Recipient sex (%males)	161/253 (63.6%)
Donor age (years)	61.70 ± 13.67
Donor sex (%males)	153/253 (60.5%)
Dialysis before transplantation	
Pre-emptive	8/253 (3.2%)
Hemodialysis	203/253 (80.2%)
Peritoneal dialysis	42/253 (16.6%)
Time on dialysis (months)	52.51 ± 50.68
Baseline cPRA (%)	15.98 ± 33.45
Diabetes mellitus	74/253 (29.2%)
Type of donor (%living)	37.5%
Donors after Brain Death	156/253 (61.7%)
Donors after Circulatory Death	97/253 (38.3%)
Induction	
No	13/253 (5.1%)
Basiliximab	143/253 (56.5%)
Anti-thymocytes globulins	97/253 (38.3%)
Immunosuppression	
TAC - MPA – PDN	82/253 (32.4%)
TAC - mTORi – PDN	171/253 (67.6%)
CIT in deceased donors (h)	14.81 ± 5.59
1-year rejection (%)	43/253 (17.0%)

cPRA, calculated panel-reactive antibodies; TAC, Tacrolimus; MPA, Mycophenolic Acid; mTORi, mTOR inhibitors, PDN, Prednisone; CIT, cold ischemia time.

When assessing dDGF and fDGF definitions criteria, 79 patients developed dDGF (31.2%) and 127 developed fDGF (50.2%). Sixty-three patients fulfilled criteria for both definitions (24.9%), while 15 patients developed dDGF but not fDGF (Fig. 1). dDGF and fDGF occurred in 21.8% and 41.7% of recipients of a DBD donor and in 46.4% and 63.9% of recipients of a DCD donor, respectively. During the follow-up, 13 grafts were lost and 45 patients died (3 after losing the graft). Taking

into account eGFR < 25 ml/min/m^2 as a surrogate endpoint for graft failure, 55 and 78 grafts were lost for death-censored graft failure (primary outcome) and for the composite outcome of graft failure or patient's death (secondary outcome), respectively.

Functional-based and Dialysis-based definition of DGF are both associated with graft failure independently of significant covariates

Univariable Cox-regression analysis demonstrated a significant correlation of both definitions with the primary [HR (95%CI) 1.90 (1.09–3.29) for fDGF and HR (95% CI) 1.83 (1.07–3.14) for dDGF, $P = 0.022$ and $P = 0.026$, respectively] and the secondary outcome [HR (95%CI) 1.72 (1.09–2.71) for fDGF and HR (95% CI) 1.61 (1.02–2.55) for dDGF, $P = 0.019$ and $P = 0.040$, respectively] (Table 2). The other covariates that were associated with the outcomes were the ECD status of the donor [HR (95%CI) 2.79 (1.40–5.56), $P = 0.003$ and 2.20 (1.28–3.78), for the primary and secondary outcomes, respectively], BPAR [HR (95%CI) 2.06 (1.14–3.74) and 1.72 (1.02–2.89), $P = 0.017$ and $P = 0.039$ for the primary and secondary outcome, respectively] and recipient age for the secondary outcome [HR (95%CI) 1.03 (1.01–1.06), $P = 0.003$ for 1-year increase] (Table 2).

When considering in a bivariable analysis all the possible combinations with these covariates, both fDGF and dDGF maintained their association with the two outcomes (Table 2).

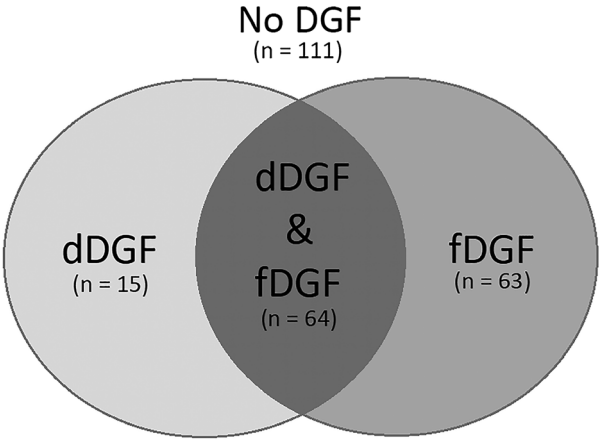

Figure 1 Venn diagram showing distribution of both DGF definitions. dDGF includes cases of isolated dDGF (i.e., without fDGF) and fDGF includes only cases of fDGF without dDGF. fDGF & dDGF includes only cases that meet the criteria for both definitions

Finally, the multivariable analysis performed with all these significant covariates demonstrated an independent association of both definitions of DGF with the primary [HR (95%CI) 2.07 (1.09–3.94), $P = 0.026$ for fDGF and HR (95%CI) 2.41 (1.33–4.37), $P = 0.004$ for dDGF] and the secondary outcome [HR (95%CI)1.58 (1.01–2.51), $P = 0.047$ for fDGF and HR (95%CI) 1.67 (1.05–2.66), $P = 0.028$ for dDGF]. No evidence for a significant interaction in the multivariable models was found between dDGF and fDGF in relation with the primary ($P = 0.501$) and the secondary outcome ($P = 0.594$).

Role of different combinations of the Functional-based and Dialysis-based definitions of DGF on graft failure at 3-year follow-up

The role of different combination of fDGF and dDGF on death-censored graft failure was explored with 3-year Kaplan–Meier survival analysis that demonstrated worst results for patients who fulfill criteria for both definitions (fDGF and dDGF) and intermediate results for patients who were fDGF+/dDGF- and fDGF-/dDGF + respectively, in comparison with the control group (Fig. 2a *P*-value for log-rank test for trend < 0.001).Three-year estimates (95%CI) of survival from death-censored graft failure (eGFR < 25 ml/min/1.73 m^2, primary outcome) were 2.83 (2.71–2.94) years for fDGF-/dDGF-, 2.63 (2.42–2.83) years for fDGF+/dDGF-, 2.47 (1.99–2.98) years for fDGF-/dDGF + and 2.31 (2.02–2.59) years for the fDGF+/dDGF + groups ($P = 0.0017$ Log-rank for trend), while 3-year estimates (95%CI) of survival from the composite outcome of eGFR < 25ml/min/1.73 m^2 or death (secondary outcome) were 2.72 (2.58–2.86) years for fDGF-/dDGF-, 2.50 (2.26–2.73) years for fDGF+/dDGF-, 2.50 (2.01–2.99) years for fDGF-/dDGF + and 2.20 (1.91–2.49) years for fDGF+/dDGF+ ($P = 0.0006$ Log-rank for trend) (Fig. 2b).

Functional DGF in the absence of dialysis-based DGF is associated with worse 1-year renal function and chronicity score at renal biopsy

A worse 1-year renal function was observed in all groups of DGF patients (43.76 ± 17.78 for fDGF+/dDGF-, 35.07 ± 12.71 for fDGF-/dDGF + and 42.78 ± 17.46 ml/min/1.73 m^2 for fDGF+/dDGF + respectively) compared to the control group (fDGF-/dDGF- 56.45 ± 21.49 ml/min/1.73 m^2), irrespective of whether fDGF or DGF were present alone or in

Table 2. Cox-regression analysis for the primary outcome (death-censored graft failure, including eGFR < 25 ml/min) and the secondary outcome (composite of graft failure, including eGFR < 25 ml/min/1.73 m^2, or recipient death)

Univariable model			Bivariable model #1			Bivariable model #2						Multivariable model #1			Multivariable model #2		
Variable	HR (95% CI)	*P*-value	Variable	HR (95% CI)	*P*-value	Variable	HR (95% CI)	*P*-value				Variable	HR (95% CI)	*P*-value	Variable	HR (95% CI)	*P*-value
Primary outcome (Graft failure, including eGFR < 25 ml/min/1.73 m^2, n = 55)																	
fDGF	1.90 (1.09–3.29)	0.022	**fDGF**	1.79 (1.03–3.11)	0.038	**fDGF**	1.77 (1.02–3.09)	0.042				**fDGF**	2.07 (1.09–3.94)	0.026	**dDGF**	2.41 (1.33–4.37)	0.004
dDGF	1.83 (1.07–3.14)	0.026	ECD status	2.67 (1.34–5.32)	0.005	1–year BPAR	1.88 (1.03–3.44)	0.038									
ECD status	2.79 (1.40–5.56)	0.003	**dDGF**	1.87 (1.09–3.20)	0.022	**dDGF**	1.75 (1.02–3.01)	0.041				ECD status	1.93 (0.92–4.05)	0.080	ECD status	2.13 (1.02–4.45)	0.044
1–year BPAR	2.06 (1.14–3.74)	0.017	ECD status	2.83 (1.42–5.63)	0.003	1–year BPAR	1.96 (1.07–3.56)	0.027				1–year BPAR	1.66 (0.84–3.25)	0.141	1–year BPAR	1.73 (0.88–4.37)	0.107
Secondary outcome (composite of graft failure, including eGFR < 25 ml/min/1.73 m^2, and recipient death, n = 78)																	
fDGF	1.72 (1.09–2.71)	0.019	**fDGF**	1.65 (1.05–2.61)	0.029	**fDGF**	1.64 (1.04–2.55)	0.033	**fDGF**	1.65 (1.05–2.61)	0.030	**fDGF**	1.58 (1.01–2.51)	0.047	**dDGF**	1.67 (1.05–2.66)	0.028
dDGF	1.61 (1.02–2.55)	0.040	ECD status	2.11 (1.24–3.68)	0.006	Age (for 1–year increase)	1.03 (1.01–1.06)	0.004	1–year BPAR	1.62 (0.96–2.73)	0.067						
ECD status	2.20 (1.28–3.78)	0.004										ECD status	1.58 (0.84–2.96)	0.152	ECD status	1.58 (0.84–2.97)	0.150
Age (for 1–year increase)	1.03 (1.01–1.06)	0.003	**dDGF**	1.63 (1.03–2.58)	0.034	**dDGF**	1.73 (1.09–2.74)	0.019	**dDGF**	1.73 (1.09–2.74)	0.058	Age (for 1–year increase)	1.02 (0.99–1.05)	0.098	Age (for 1–year increase)	1.02 (.99–1.05)	0.060
1–year BPAR	1.72 (1.02–2.89)	0.039	ECD status	2.22 (1.29–3.82)	0.004	Age (for 1–year increase)	1.04 (1.01–1.06)	0.002	1–year BPAR	1.65 (0.98–2.77)	0.059	1–year BPAR	1.48 (0.88–2.51)	0.139	1–year BPAR	1.50 (0.89–2.53)	.126

The functional– (fDGF) and dialysis–based (dDGF) were analyzed as well as significant covariates in univariable, bivariable and multivariable models. The multivariable model included ECD status and BPAR for the primary outcome and ECD status, BPAR and age for the secondary outcome. *ECD*, Expanded Criteria Donor, *BPAR*, Biopsy–Proven Acute Rejection.

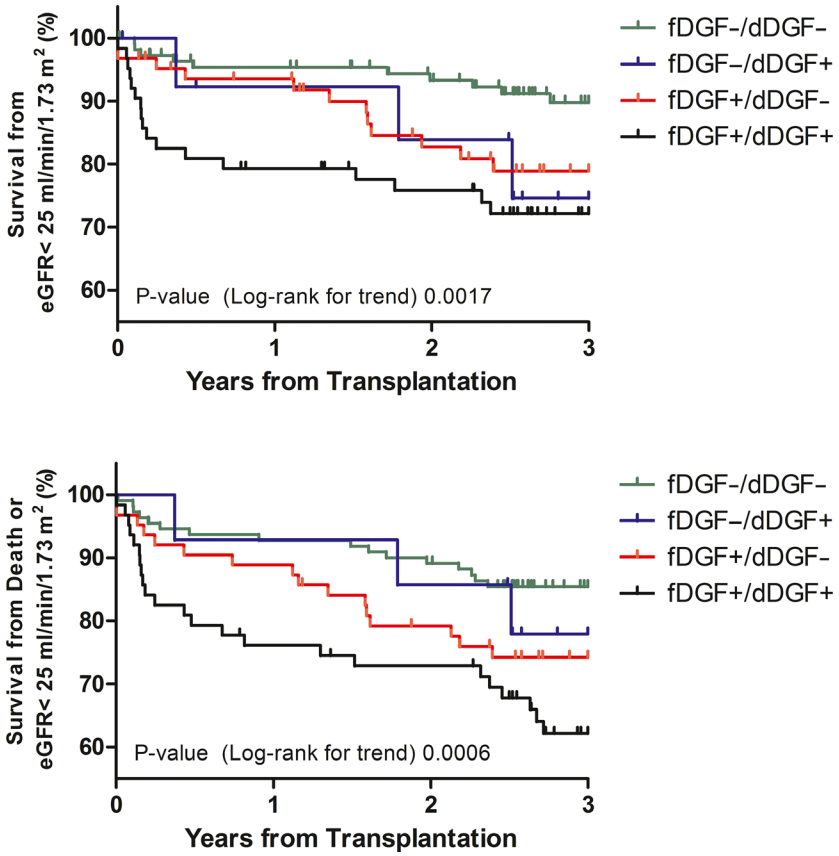

Figure 2 (a) Kaplan–Meier estimates of survival for 3–year freedom from death–censored graft failure, including eGFR < 25 ml/min/1.73 m^2. (b) Kaplan–Meier estimates of survival for 3–year freedom from the composite outcome of graft failure, including eGFR < 25 ml/min/1.73 m^2, or recipient's death

combination ($P < 0.001$) (Table 3). Moving to chronicity scores at 1-year protocol kidney biopsies, patients with dDGF and fDGF (fDGF+/dDGF+) had worse results for interstitial fibrosis (ci) and tubular atrophy (ct) in comparison with the control group (*ci* 1.55 ± 1.00 versus 0.93 ± 0.68 and *ct* 1.55 ± 1.00 versus 1.00 ± 0.61, respectively, both $P = 0.001$), while there were no differences in terms of vascular fibrous intimal thickening (cv) and glomerular basement membrane double contours (cg)(Table 3).

Table 3. One–year analysis of eGFR and chronicity score values at protocol renal biopsy according to ANOVA test. Post hoc analysis (LSD) was performed among groups

	Group 1* dDGF– fDGF– (*n* = 111)	Group 2** dDGF+ fDGF– (*n* = 15)	Group 3*** dDGF– fDGF+ (*n* = 63)	Group 4**** dDGF+ fDGF+ (*n* = 64)	*P*–value (ANOVA)
1–year eGFR (ml/min/1.73 m^2)	56.45 ± 21.49**,***^	35.07 ± 12.71*	43.76 ± 17.78*	42.78 ± 17.46*	<0.001
Ci	0.93 ± 0.68****	1.00 ± 0.57	1.22 ± 0.86	1.55 ± 1.00*	0.008
Ct	1.00 ± 0.61****	1.14 ± 0.37	1.17 ± 0.81****	1.55 ± 1.00*,**	0.016
Cv	1.08 ± 0.81	1.14 ± 0.69	0.97 ± 0.63	1.16 ± 0.72	0.785
Cg	0.02 ± 0.12	0.14 ± 0.37	0.03 ± 0.16	0.06 ± 0.24	0.324

*$P < 0.05$ when compared to group 1.

**$P < 0.05$ when compared to group 2.

***$P < 0.05$ when compared to group 3.

****$P < 0.05$ when compared to group 4.

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Factors associated with the development of functional- and dialysis-based definitions of DGF

Donor and recipient factors associated with the occurrence of fDGF and dDGF were explored in a logistic regression model (Table 4). For both definitions, donor after circulatory death (DCD) was associated with both definitions of DGF [OR (95%CI) for DCD 2.48 (1.47–4.18), $P = 0.001$, and 3.10 (1.79–5.38), $P < 0.001$, for fDGF and dDGF, respectively]. Also donor male sex was associated with both fDGF and dDGF [OR (95%CI) 1.72 (1.03–2.87), $P = 0.036$, and 2.10 (1.18–3.74), $P = 0.011$, for fDGF and dDGF respectively] (Table 4).

Discussion

In kidney transplantation, the functional definition of DGF (fDGF) has the potential to be more objective than the dialysis-based definition (dDGF), which is subjected to the physician's clinical practice and hospital policy. However, studies that analyzed the performance of both definitions for hard outcomes, such as graft failure (censored or not by death), gave controversial results [8–10,15]. Boom et al [10] was the first to analyze the fDGF definition in a retrospective series of 734 renal transplant recipients from deceased donors. fDGF was present in 183 patients (23.2%), whereas dDGF was present in 244 (33.9%), but only fDGF outcomes were analyzed. The multivariable analysis revealed that fDGF was a risk factor for suboptimal graft function within the first year. However, when assessing the influence of fDGF on 1-year death-censored graft failure it was not significantly associated with the outcome [10]. Ten years later, Moore et al [8] prospectively compared the performances of both definitions, assessing 750 kidney transplant recipients from deceased donors. fDGF was present in 286 patients (38%), whereas dDGF was present in 255 (34%). When dDGF and fDGF were examined in a bivariate and multivariable analysis, only fDGF was significantly associated with an increased rate of death-censored and overall graft failure rates, being the presence of both fDGF and dDGF the combination with the worst prognosis [8]. It has to be highlighted that in both studies mean donor and recipient age were lower than 50 years, and immunosuppression was cyclosporine- and azathioprine-based; a clinical setting that is far different from the actual one in kidney transplantation.

Our study, on turn, was based on a modern series of kidney transplants, with a mean age of donors and recipients of 61.21 ± 10.73 and 61.70 ± 13.67 years respectively, which is higher than previous studies [8–10,15] and with a baseline immunosuppression based on tacrolimus associated with either mycophenolate or mTOR inhibitors, a scenario that is closer to the current one in Europe and U.S. [11,12,18]. Importantly, and in contrast from previous studies [9,15], we analyzed the impact of fDGF and dDGF for poor graft function, expressed as the freedom from < 25 ml/min/1.73 m^2 (including graft failure) in the primary outcome and also patient's death in the secondary one. We found that both definitions (fDGF and dDGF) were significantly associated with both outcomes, an association that was maintained even after adjustment for relevant confounding factors in bivariable and multivariable analysis. A relevant point is that any combination of fDGF and dDGF proved to be associated with both outcomes, with patients fulfilling criteria for both definitions having the worst results (Fig. 2). All the different scenarios are graphically represented in Fig. 3.

Our results are somewhat different from those recently reported by Hall et al [9], who analyzed the mean 12-months eGFR for different not dialysis-based

Table 4. Analysis of common risk factors for the development of **fDGF** and **dDGF** by logistic regression analysis

	fDGF		dDGF	
	OR (95% CI)	*P*–value	OR (95% CI)	*P*–value
Type of donor (DCD vs DBD)	2.48 (1.47–4.18)	**0.001**	3.10 (1.79–5.38)	**<0.001**
Recipient sex (M vs F)	1.33 (0.79–2.22)	0.275	1.74 (0.97–3.10)	0.059
Donor sex (M vs F)	1.72 (1.03–2.87)	**0.036**	2.10 (1.18–3.74)	**0.011**
ECD status	1.44 (0.85–2.44)	0.169	1.20 (0.68–2.13)	0.521
Previous transplant	0.57 (0.30–1.07)	0.081	0.79 (0.40–1.57)	0.516
Cold ischemia time> 24h	0.34 (0.10–1.10)	0.072	0.76 (0.23–2.47)	0.648

OR, Odds ratio, CI, Confidence Interval, DBD, Donors after Brain Death, DCD, Donors after Circulatory Death, ECD, Expanded Criteria Donor, CIT, Cold Ischemia time; F, female; M, Male.

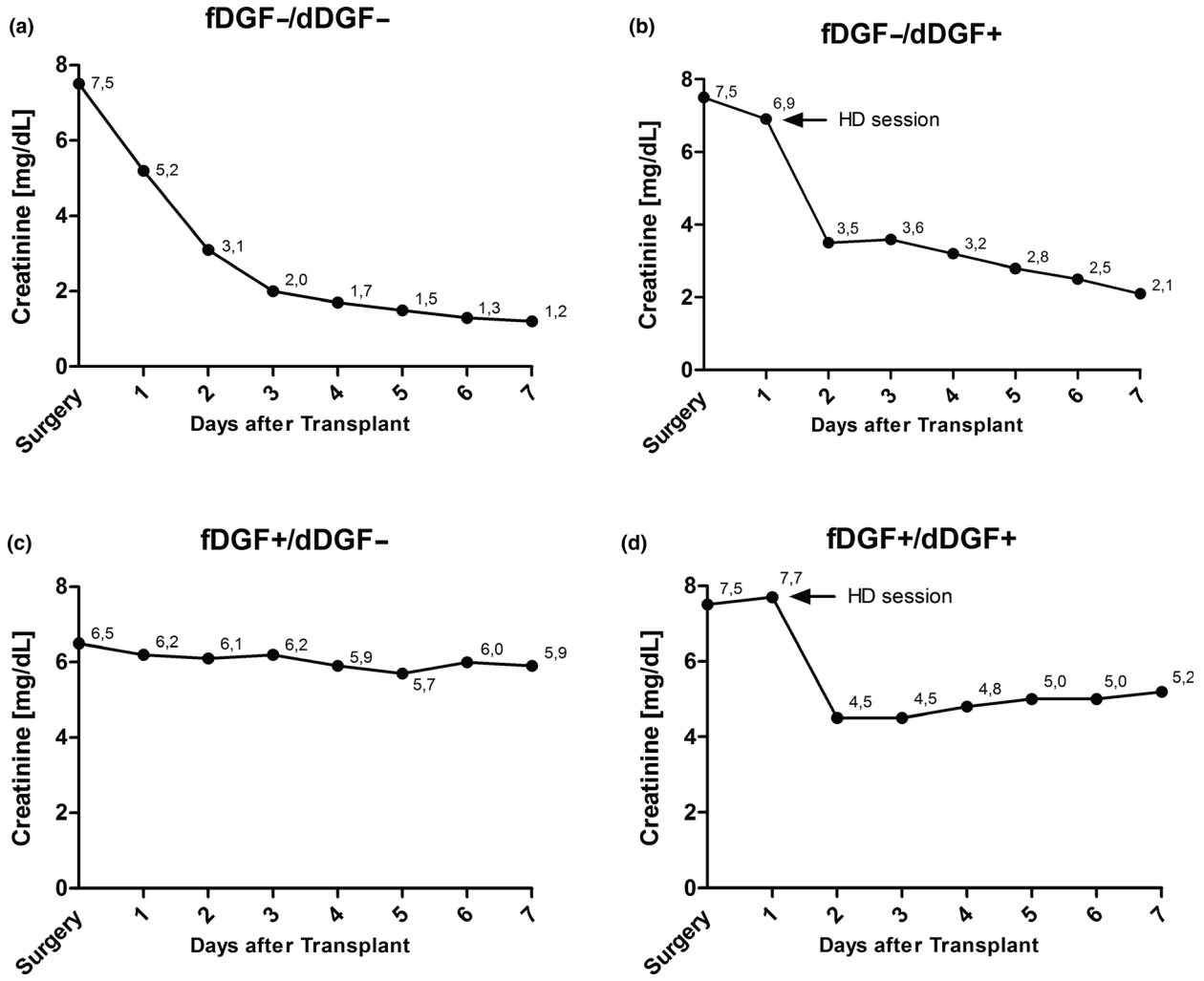

Figure 3 Graphical representation of the different scenarios that can occur during the first week after kidney transplantation. Patients who do not develop either fDGF or dDGF have expectably the best outcome (a). Patients submitted to dialysis after transplantation but recover rapidly renal function afterward have a favorable outcome as well (b). On turn, patients who do not receive dialysis but whose renal function does not improve after transplant are a population at risk (c). The worst case scenario is represented by patients who receive dialysis and afterward renal function still does not improve; that is, they fulfill both definitions of DGF (dialysis– and functional–based)

DGF definitions, among which was the fDGF definition proposed by Boom et al [10]. Nevertheless, this definition was not associated with poor 12-months outcomes compared to those patients without DGF (i.e., neither fDGF nor dDGF) and with dDGF. However, in this study the fDGF definition was only compared with the dDGF for the absolute eGFR value at 12 months, but an analysis of the specific contribution of each definition (individually and combined) for eGFR, death-censored and overall graft failure, as well as of the recipient and donor factors potentially associated with fDGF was not performed [9].

In another recent study, Hu et al [15] analyzed the predictive value of up to 6 different DGF definitions (including the dDGF definition and that proposed by Boom et al [10]) for overall and death-censored graft loss at 3 years. They observed that all of DGF definitions predicted the outcome, although the fDGF definition presented one of the lowest predictive values [15]. However, only DCD donors were included, so the performance of fDGF on DBD donors was not evaluated. In fact, in the present study we evidenced that in the adjusted models fDGF presented a significant correlation for both outcomes, independently of the donor type. This suggests that fDGF would probably be a useful prognostic marker for long-term graft function, especially in kidney grafts from DBD donors, in which the need for post-transplant dialysis is less frequent than in transplants from DCD donors, and in which the dDGF definition could not entirely identify patients at

risk of poor graft outcomes [19]. Moreover, the incidence of ECD in the study of Hu et al was relatively low (10% of the entire cohort), a factor that, as we showed in the present study, seems to increase the risk of fDGF [15].

A key aspect in this kind of studies is the immunosuppressive regimen of the included patients, which in most cases was not specified in terms of type of immunosuppressants or its distribution among the studied groups [9,15]. This is an important issue taking into account that cyclosporine has been associated with higher nephrotoxicity and poorer eGFR than tacrolimus [13,20–22] in the long-term follow-up, as well as the increasing use of CNI-minimization strategies with mTORi [13,20–22].

Another point worth of attention is represented by the worse renal function observed in patients with any combination of fDGF and dDGF compared to the control group. Furthermore, 1-year chronicity scores at protocol kidney biopsies were worse in those patients who fulfilled criteria for both definitions. This is likely helpful to better stratify patients with DGF for suboptimal renal function at medium-term follow-up.

Regarding donor and recipient factors associated with dDGF and fDGF, as previously reported [23], DCD donors were associated with a higher incidence of fDGF and dDGF. ECD status was not associated with an increased risk, while donor and recipient male sex proved to be significant risk factors for fDGF and dDGF.

The limitations of our study are mainly its retrospective and monocentric nature. It would be desirable in the future to rely on multicentric data to increase the studied population and to analyze more thoroughly the performance of the different combinations of the two definitions on long-term hard outcomes. Moreover, follow-up time was relatively short (3.22 [2.38–4.21] years), so the results were focused on freedom from eGFR < 25 ml/min/1.73 m^2 and not solely on graft failure. It would be interesting in future studies to reassess results with a larger follow-up, focusing specifically only on graft failure. On turn, the most important strength relies on the reassessment of the fDGF definition in the new landscape of kidney transplantation, in which elderly donors are more common and baseline immunosuppression is no longer cyclosporine-based. A point of value is a face-to-face comparison of the different combinations of fDGF and dDGF definitions regarding graft failure, eGFR, histological chronicity scores and the assessment of risk factors associated with the two definitions.

In conclusion, fDGF is a condition with important repercussion on graft survival. The characteristics of this definition could help to early identify kidney transplant recipients who suffer from intense ischemia-reperfusion injury and who are at risk of developing worse long-outcomes. In this regard, fDGF alone and/or its combination with the dialysis-based definition may be more sensitive as a short-term outcome in clinical trials about cadaveric donor and graft management.

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Author contribution

EMM participated in the performance of the research and writing of the paper. AMA participated in the performance of the research and writing of the paper. JRovira/GP/IR/PVA/NE/FC/JUA/ JMC/AGH/ FO/JVT/EDS critically revised the manuscript. JRíos participated in data analysis and writing of the paper. FD participated in manuscript design and revised it critically. DC participated in manuscript design, data analysis and writing of the paper.

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REFERENCES

1. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. *Lancet* 2004; **364**: 1814.
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. Grosso G, Corona D, Mistretta A, *et al*. Delayed Graft Function and Long-Term Outcome in Kidney Transplantation. *Transplant Proc* 2012; **44**: 1879.
4. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997; **63**: 968.
5. 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.
6. Redfield RR, Scalea JR, Zens TJ, *et al*. Predictors and outcomes of delayed graft function after living-donor kidney transplantation. *Transpl Int* 2016; **29**: 81.
7. 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.
8. Moore J, Shabir S, Chand S, *et al*. Assessing and Comparing Rival Definitions of Delayed Renal Allograft Function for Predicting Subsequent Graft Failure. *Transplantation* 2010; **90**: 1113.
9. Hall IE, Reese PP, Doshi MD, *et al*. Delayed Graft Function Phenotypes and 12-Month Kidney Transplant Outcomes. *Transplantation* 2017; **101**: 1913.
10. 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.
11. Actividad de donación y trasplante renal España 2019. Organización Nacional de Trasplantes. http://www.ont.es/infesp/Memorias/Actividadde DonaciónyTrasplante Renal.pdf. Accessed April 14, 2019.
12. Hart A, Smith JM, Skeans MA, *et al*. OPTN/SRTR 2018 Annual Data Report: Kidney. *Am J Transplant* 2020; **20**: 20.
13. Pascual J, Berger SP, Witzke O, *et al*. Everolimus with Reduced Calcineurin Inhibitor Exposure in Renal Transplantation. *J Am Soc Nephrol* 2018; **29**: 1979.
14. Ekberg H, Bernasconi C, Tedesco-Silva H, *et al*. Calcineurin Inhibitor Minimization in the Symphony Study: Observational Results 3 Years after Transplantation. *Am J Transplant* 2009; **9**: 1876.
15. Hu X, Zheng J, Li Y, *et al*. Prediction of kidney transplant outcome based on different DGF definitions in Chinese deceased donation. *BMC Nephrol* 2019; **20**: 409.
16. Cucchiari D, Ríos J, Molina-Andujar A, *et al*. Combination of calcineurin and mTOR inhibitors in kidney transplantation: a propensity score analysis based on current clinical practice. *J Nephrol* 2020; **33**: 601.
17. Haas M, Loupy A, Lefaucheur C, *et al*. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant* 2018; **18**: 293.
18. Johnson RJ, Bradbury LL, Martin K, Neuberger J. Organ donation and transplantation in the UK-The last decade: A report from the UK national transplant registry. *Transplantation* 2014; **97**: S1.
19. Summers DM, Watson CJE, Pettigrew GJ, *et al*. Kidney donation after circulatory death (DCD): state of the art. *Kidney Int* 2015; **88**: 241.
20. Cucchiari D, Molina-Andujar A, Montagud-Marrahi E, *et al*. Use of De Novo mTOR Inhibitors in Hypersensitized Kidney Transplant Recipients: Experience From Clinical Practice. *Transplantation* 2020; **104**: 1686.
21. Nankivell BJ, Ng CHP, O'Connell PJ, Chapman JR. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: Comparison of cyclosporine and tacrolimus eras. *Transplantation* 2016; **100**: 1723.
22. Shihab FS, Waid TH, Conti DJ, *et al*. Conversion from cyclosporine to tacrolimus in patients at risk for chronic renal allograft failure: 60-Month results of the CRAF study. *Transplantation* 2008; **85**: 1261.
23. Locke JE, Segev DL, Warren DS, Dominici F, Simpkins CE, Montgomery RA. Outcomes of Kidneys from Donors After Cardiac Death: Implications for Allocation and Preservation. *Am J Transplant* 2007; **7**: 1797.