ORIGINAL ARTICLE

Exploring the causes of the high incidence of delayed graft function after kidney transplantation in Brazil: a multicenter study

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SUMMARY

This retrospective multicenter ($n = 18$) cohort study evaluated the incidence, risk factors, and the impact of delayed graft function (DGF) on 1-year kidney transplant (KT) outcomes. Of 3992 deceased donor KT performed in 2014–2015, the incidence of DGF was 54%, ranging from 29.9% to 87.7% among centers. Risk factors ($_{\text{lower-bound-95\%CI}}$ OR $_{\text{upper-bound-95\% CI}}$) were male gender ($_{1.066}1.249_{1.463}$), diabetic kidney disease ($_{1.053}1.296_{1.595}$), time on dialysis ($_{1.005}1.007_{1.009}$), retransplantation ($_{1.035}1.397_{1.885}$), preformed anti-HLA antibodies ($_{1.011}1.383_{1.892}$), HLA mismatches ($_{1.006}1.066_{1.130}$), donor age ($_{1.011}1.017_{1.023}$), donor final serum creatinine (sCr) ($_{1.239}1.317_{1.399}$), cold ischemia time (CIT) ($_{1.031}1.043_{1.056}$), machine perfusion ($_{0.401}0.542_{0.733}$), and induction therapy with rabbit antithymocyte globulin (rATG) ($_{0.658}0.800_{0.973}$). Duration of DGF > 4 days was associated with inferior renal function and DGF > 14 days with the higher incidences of acute rejection, graft loss, and death. In conclusion, the incidence and duration of DGF were high and associated with inferior graft outcomes. While late referral and poor donor maintenance account for the high overall incidence of DGF, variability in donor and recipient selection, organ preservation method, and type of induction agent may account for the wide variation observed among transplant centers.

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Introduction

The incidence of delayed graft function (DGF) varies across different regions of the continents. In the United States, the reported incidence is around 30%, even when donation after cardiac death (DCD) is considered [1,2]. In European centers, this incidence ranges from 30 to 35% [3,4] and is higher, between 35 to 45%, among countries participating in the European Senior Transplant Program [5,6]. Finally, in Australia and New Zealand, the reported incidence of DGF is around 25% [7].

Single-center Brazilian studies have shown incidences of DGF varying from 54.2% to 82% [8–12]. This disproportionally higher incidence is not explained by crude demographic characteristics as all kidney transplants are from brain-dead deceased donors and the proportion of expanded criteria donors (ECD) does not exceed 30%. The diversity of recipient and donor demographic characteristics and the lack of uniformity in DGF definitions hinder the understanding of the real Brazilian scenario. A multicenter Brazilian study including 6 transplant centers located in the South and Southeast Regions of the country reported an incidence of 55.6%. Nevertheless, DGF was not clearly defined, limited information on demographics was available, and the study included kidney transplants (KT) performed from 2000 to 2002. Certainly, organ acceptance policies and clinical practices have changed since then [13].

Importantly, these previous reports do not provide reliable evidence regarding the risk factors association with this high incidence of DGF, and nonclassical donor-related variables probably contributed to these results [8–12]. Using a standardized DGF definition, this multicenter study aimed to determine the national rate of DGF and its duration, the associated risk factors, and the impact on short-term kidney transplant outcomes.

Patients and methods

Study design

Center selection

This was a multicenter, national, retrospective cohort study, including deceased donor (DD) KT performed between Jan 2014 and Dec 2015.

Objectives

This analysis had three prespecified objectives: (i) to determine the national incidence and duration of DGF; (ii) to identify the risk factors associated with DGF and duration of DGF; (iii) to determine the influence of DGF and duration of DGF on 1-year kidney transplant outcomes.

Population

The study included all consecutive kidney transplants performed in each participating center. Recipients younger than 18 years, combined and preemptive transplants, were excluded. For this analysis, recipients who lost the graft for any reason or died within 7 days, who lost the graft within 30 days due to vascular thrombosis, and who presented primary nonfunctioning grafts were also excluded.

Ethical considerations

The study was reviewed and approved by the Institutional Review Board (IRB) of Federal University of Ceará, from where the study was coordinated (approval number 2.108.244). All participating centers also obtained local IRB approval before data collection. The obtaining of informed consent or its exemption occurred following the guidelines of the Declaration of Helsinki, specific national legislations, and local IRB recommendations. Patient records and information were anonymized and de-identified before analysis.

Transplant outcomes

The 12-month outcomes of interest for this analysis were the incidence of DGF, the duration of DGF, the incidence of treated acute rejection (tAR), treated biopsy-proven acute rejection (tBPAR), and tBPAR including borderline changes, the proportion of patients with estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2, the proportion of patients with eGFR <50 ml/min/1.73 m^2 or tBPAR, the cumulative incidences of death-censored graft loss and death at 12 months.

Definitions

DGF was defined as the requirement for at least one dialysis session during the first week after KT, excluding once-off dialysis sessions performed at immediate postoperative day due to hypervolemia or hyperkalemia [14]. DGF duration was assessed by the time until the last dialysis session. ECD was defined using United Network for Organ Sharing definition [15]. Kidney Donor Profile Index (KDPI) [16] was calculated using "ktx.kdpi.optn," an R open source programming code [17]. tAR included all episodes of acute allograft dysfunction, treated with methylprednisolone and/or rabbit antithymocyte globulin (rATG), regardless of biopsy. tBPAR excluded borderline changes (suspicious for rejection), according to Banff 2018 classification [18]. Renal function: eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Death-censored graft loss was defined as the return to long-term dialysis therapy or retransplantation.

Statistical analysis

Data were entered in a case report form specifically designed for this analysis using the RedCap platform. Categorical variables were presented as frequency and percentage and compared using Chi-square or Fisher tests. Normally distributed continuous variables were summarized as mean and standard deviation. Non-normally distributed continuous variables were summarized as median and interquartile range (IQR). eGFR at 12 months was calculated using the "Last Observation Carried Forward" imputation method. For patients with missing eGFR values at 12 months, zero was attributed to patients who lost the graft and the last available eGFR for those who died or lost the follow-up. Survival curves were obtained using Kaplan–Meier method and compared using the log-rank test. Multivariable analyses to identify independent risk factors associated with DGF, eGFR <50 ml/min/1.73 m^2, eGFR <50 ml/min/1.73 m^2 or tBPAR, death-censored graft loss and death (binary variable) were performed using Generalized Linear Mixed Model (GLMM) with Logistic Regression, adjusted for transplant center/site (random effect), and discrimination performance was tested using the Area Under the Receiver Operating Curve (AUC-ROC). Multivariable analysis for risk factors for the duration of DGF (discrete numeric variable) was performed using GLMM with Negative Binomial Regression, adjusted for transplant center/site (random effect), and discrimination performance was tested using the comparison between predicted and observed values. For this analysis, the dispersion parameter φ was 19.905 (larger than 1), indicating overdispersion and supporting the use of a negative binomial model over a Poisson model. For patients who did not present DGF, time on DGF was considered 0 (zero). All available variables were considered relevant and were included in the multivariable model regardless of their significance in bivariate analysis. Collinear variables and those with more than 10% of missing values were excluded from multivariable models. The significantly statistical difference was assumed when the p value was less than 0.05.

Results

Population and demographics

Between Jan 2014 and Dec 2015, 8657 single DD KT were performed in 125 transplant centers [19,20]. Twenty-three sites accepted the invitation to participate in this study, 19 obtained the ethical approvals within the proposed deadline and, finally, 18 inserted their data in the electronic case report form in a timely manner. The 18 included sites performed 4156 single DD KT in adult recipients during the period. After excluding

preemptive KT ($n = 41$), graft losses for other causes and deaths within 7 days ($n = 79$), vascular thrombosis within 30 days ($n = 27$), and primary nonfunctioning grafts ($n = 17$), 3992 patients were included in the final study cohort. The 18 sites that participated in this study are located in the South, Southeast, and Northeast of Brazil. DGF was observed in 2157 patients (54%). Baseline recipient and donor characteristics are shown in Table 1.

DGF incidence and duration

The incidence of DGF ranged from 29.9% to 87.7% among KT sites (Fig. 1). There was no apparent association between the incidence of DGF and the country region. The incidence of DGF was lower among recipients of standard versus expanded criteria donors (51.1% vs. 62%, $P < 0.001$). The incidence of DGF was 46% among patients receiving kidneys from donors with KDPI ≤47% (percentile 25) and 44.4% among those with cold ischemia time (CIT) ≤17h (percentile 25). The mean time on DGF was 12.2 ± 14.7 days (median 8, IQR 4–14 days, range 1–220 days), and the mean number of dialysis sessions performed during this period was 4.6 ± 4.8 (median 3, IQR 2–6, range 1–93) (Fig. 2).

Risk factors for DGF and for time on DGF

Multivariable analysis demonstrated that recipient male gender, diabetic end-stage kidney disease (ESKD), time on dialysis, retransplantation, preformed anti-Human Leukocyte Antigens (HLA) donor-specific antibodies (DSA) higher than 1500 mean intensity fluorescence, HLA mismatches, donor age, donor final serum creatinine (sCr), and CIT were risk factors independently associated with increased risk of DGF. In contrast, machine perfusion and the use of rATG induction were associated with reduced risk of DGF. Similarly, time on dialysis, retransplantation, HLA mismatches, donor male gender, donor age, donor final sCr, CIT, and initial immunosuppressive with mammalian target of rapamycin inhibitors (mTORi) were risk factors associated with increased duration of DGF, whereas the use of rATG induction was associated with reduced duration of DGF (Table 2, Tables S1, and S2).

Association of DGF with transplant outcomes

DGF was associated with at least 1.89-times higher risk of inferior transplant outcomes compared to Non-DGF (Fig. 3). Patients with DGF had higher incidence of tAR (20.6% vs. 9.2%, $P < 0.001$), tBPAR and borderline changes (17% vs. 6.9%, $P < 0.001$), tBPAR (10.3% vs. 4.5%, $P < 0.001$) and shorter time to first tBPAR (48.5 ± 70.8 days, median 18 days, IQR 11–51.5 days vs. 90.3 ± 101.8 days, median 43 days, IQR 16.5–131.5 days, $P < 0.001$). The majority of tBPAR was Banff I (59.2%), with 21.6% Banff II/III and 21.6% antibody-mediated rejections or mixed rejections. There were no differences in the Banff categories between the groups ($P = 0.376$).

At 12 months, the proportion of patients with eGFR < 50 ml/min/1.73 m^2 and with eGFR < 50 ml/min/1.73 m^2 or tBPAR was higher in the DGF group. Mean eGFR was inferior in DGF group (57.7 ± 26.4 ml/min/1.73 m^2, median 56.4, IQR 39–75.1 ml/min/1.73 m^2 vs. 47.1 ± 25.2 ml/min/1.73 m^2, median 46.8, IQR 29.5–62.9 ml/min/1.73 m^2, $P < 0.001$).

One-year death-censored graft survival (97.5% vs. 95%, $P < 0.001$) and patient survival (97.4% vs. 94.1%, $P < 0.001$) were inferior in patients who developed DGF. Graft losses occurred at a mean time of 139.5 ± 98.5 days (median 112 days, IQR 55–214 days). The main causes were acute rejection (25.3%), interstitial fibrosis/tubular atrophy (18%), acute pyelonephritis (16%), vascular lesions (12.7%), and urological/technical complications (8.7%), with no differences between the groups ($P = 0.160$). Deaths occurred at a mean time of 136.6 ± 104.6 days (median 104 days, IQR 47–210 days). The main causes were infection (63.6%) and cardiovascular events (20.2%) ($P = 0.931$).

Association of the duration of DGF with transplant outcomes

Transplant outcomes were compared between the Non-DGF group and quartile distribution of DGF duration (1–4 days, 5–8 days, 9–14 days, >14 days). A trend between increasing incidence of transplant outcomes and increasing duration of DGF was observed (Fig. 4). DGF duration was associated with an increasing proportion of patients with eGFR lower than 50 ml/min/1.73 m^2 and with the composite outcome of eGFR lower than 50 ml/min/1.73 m^2 or tBPAR. For tBPAR, statistical difference was observed when DGF duration longer than 8 days while for death-censored graft loss and death, this association was observed when DGF was longer than 14 days (Fig. 4). Compared with Non-DGF group, median eGFR at 1 year was inferior in all DGF groups (Non-DGF: 56; DGF 1–4 days: 49.9; DGF 5–

Table 1. Recipient demographics and initial immunosuppression.

	Nonmissing cases	Total $n = 3992$
Recipient		
Age (years old)	3992	49.4 (38.5–58.4)
Gender—male	3992	2505 (62.8)
Race	3910	
Caucasian		1984 (50.7)
Mixed race		1346 (34.4)
Afro-Brazilian		536 (13.7)
Asian/Indian		44 (1.1)
Recipient BMI (kg/m^2)	3545	24.4 (21.7–27.5)
ESKD etiology	3992	
Unknown		1149 (28.8)
Hypertension		752 (18.8)
Diabetes*		714 (17.9)
Chronic GN		621 (15.6)
Other		756 (18.9)
Time on dialysis (months)	3991	35.8 (19–60.8)
Retransplantation	3992	304 (7.6)
PRA I (%)	3966	0 (0–8)
PRA II (%)	3893	0 (0–0)
Preformed DSA > 1500 MFI	3885	264 (6.8)
HLA MM	3963	3 (2–4)
rATG induction	3990	2672 (67)
CNI-free or late introduction*	3992	1183 (29.6)
de novo mTORi	3992	513 (12.9)
Donor		
Age (years old)	3992	45 (31–54)
Gender—male	3963	2377 (60)
Race	3059	
Caucasian		1536 (50.2)
Mixed race		1144 (37.4)
Afro-Brazilian		363 (11.9)
Asian		16 (0.5)
BMI (kg/m^2)	3418	25.4 (24–27.6)
Hypertension	3492	1113 (31.9)
Diabetes	3767	216 (5.7)
Cause of death	3837	
Cerebrovascular		2087 (54.4)
Trauma		1530 (39.9)
Anoxia/Tumor		220 (5.8)
Final sCr (mg/dl)	3983	1.3 (0.9–2.1)
ECD	3992	1068 (26.8)
KDPI (%)	3882	65 (47–82)
Reversed cardiac arrest	3988	576 (14.4)
Vasoactive drug use	3952	3509 (88.8)
Multiple organ donor	3047	2820 (92.6)
Perfusion solution	3620	
Eurocollins		1837 (50.7)
Custodiol-HTK		1088 (30.1)
IGL-1		486 (13.4)
Belzer-UW		59 (1.6)
Other		150 (4.1)
Machine perfusion	3991	345 (8.6)
CIT (h)	3978	21.7 (17–26.1)
VAT (min)	3387	30 (23–40)

All continuous variables have non-normal distribution and were presented as median and interquartile range.

BMI, body mass index; ESKD, end-stage kidney disease; GN, glomerulonephritis; PRA, panel reactive antibodies; DSA, donor-specific anti-HLA antibodies; MFI, mean intensity fluorescence; HLA, human leukocyte antigen; MM, mismatches; rATG, rabbit antithymocyte globulin; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor; sCr, serum creatinine; ECD, expanded criteria donor; CIT, cold ischemia time; VAT, vascular anastomosis time.

*After 48 h posttransplant.

8 days: 48.7; DGF 9–14 days: 49.9; DGF > 14 days: 37.8 ml/min/1.73 m^2, $P < 0.001$).

Multivariable analysis for the impact of DGF on KT outcomes

After the adjustment for confounding variables, DGF was independently associated with tBPAR (OR 1.757, 95%CI 1.350–2.228, $P < 0.001$) and inferior renal function at 1 year (OR 2.444 95%CI 1.801–3.316, $P < 0.001$), but not with death-censored graft loss or death (Table S3).

Multivariable analysis for the impact of quartiles of time on DGF on KT outcomes

Adjusting the impact of quartiles of time on DGF for confounding variables, only DGF longer than 14 days was associated with tBPAR, death-censored graft loss and death. DGF longer than 4 days was associated with inferior renal function and with the composite outcome, inferior renal function or tBPAR (Table 3 and Table S4).

Discussion

The key finding of this multicenter study is the high incidence of DGF among KT recipients from all geographical regions, regardless of the donor quality and cold ischemia time. These data corroborate with and expand previous single-center studies [8–12] and also show that DGF duration has a negative impact on graft

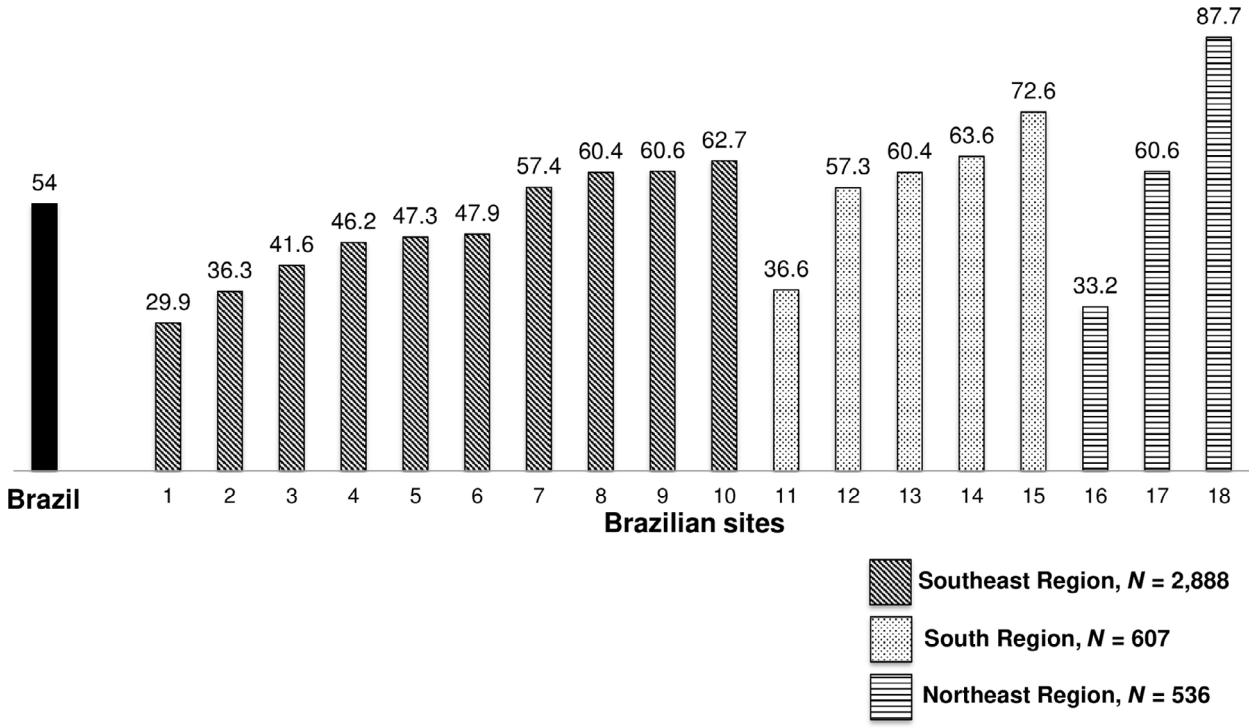

Figure 1 Delayed graft function incidence in Brazil and Brazilian sites.

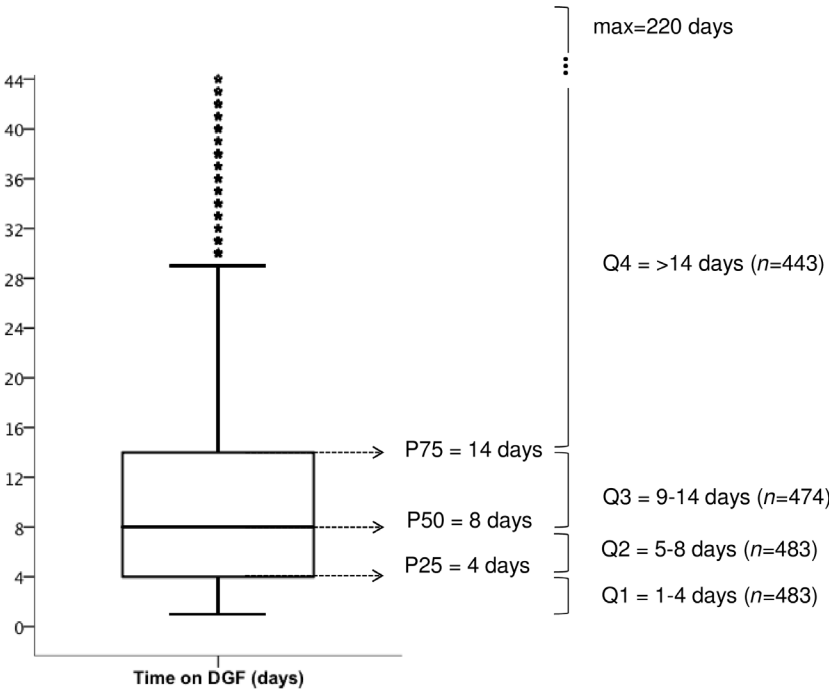

Figure 2 Duration and quartiles of time on delayed graft function. P: percentile; Q: quartile. Extreme outliers were excluded from the boxplot graph. 274 patients who presented DGF had no information on duration.

outcomes already detected at one year after transplantation. The known risk factors associated with the incidence and duration of DGF were also identified in our analysis, with time on dialysis, CIT, machine perfusion, and immunosuppressive strategies among those potentially modifiable.

Previous studies have suggested that the time on dialysis before KT is a risk factor for DGF [9,21]. While time on dialysis is associated with the allocation system, immediate wait-listing and reduction of time off wait-list for any reason are two feasible strategies. Unfortunately, as we did not capture these data for this current

Table 2. Risk factors for DGF and time on DGF.

DGF (yes/no)#,†	DGF *N* = 1653	Non-DGF *N* = 1403	OR (95% CI)	*P* value
Recipient gender—male	1071	845	1.249 (1.066–1.463)	0.006
Diabetic ESKR	308	218	1.296 (1.053–1.595)	0.014
Time on dialysis (months)	1653	1403	1.007 (1.005–1.009)	<0.001
Retransplantation	145	95	1.397 (1.035–1.885)	0.029
Preformed DSA > 1500 MFI	130	86	1.383 (1.011–1.892)	0.042
HLA MM	1653	1403	1.066 (1.006–1.130)	0.031
Donor age (years old)	1653	1403	1.017 (1.011–1.023)	<0.001
Donor final sCr (mg/dL)	1653	1403	1.317 (1.239–1.399)	<0.001
CIT (h)	1653	1403	1.043 (1.031–1.056)	<0.001
Machine perfusion	142	164	0.542 (0.401–0.733)	<0.001
rATG induction	1147	964	0.800 (0.658–0.973)	0.026

Time on DGF (days)£, §, †	Total *n* = 2849			
	DGF *N* = 1446	Non-DGF *N* = 1403	IRR (95% CI)	*P* value
Time on dialysis (months)	2849		1.002[a] (1.000–1.004)	0.012
Retransplantation	209		1.415[b] (1.053–1.902)	0.021
HLA MM	2849		1.083[a] (1.023–1.147)	0.006
Donor gender—male	1743		1.204[b] (1.019–1.422)	0.029
Donor age (years old)	2849		1.010[a] (1.004–1.016)	0.001
Donor final sCr (mg/dL)	2849		1.064[a] (1.009–1.122)	0.021
CIT (h)	2849		1.023[a] (1.011–1.034)	<0.001
rATG induction	2035		0.714[b] (0.586–0.869)	0.001
de novo mTORi	412		1.330[b] (1.056–1.676)	0.016

DGF, delayed graft function; ESKD, end-stage kidney disease; DSA, donor-specific anti-HLA antibodies; MFI, mean intensity fluorescence; sCr, serum creatinine; HLA MM, human leukocyte antibodies mismatches; CIT, cold ischemia time; rATG, rabbit antithymocyte globulin; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor; OR, odds-ratio; IRR, incidence rate ratio; CI, confidence interval.

†Variables included in the model: gender, recipient age, Afro-Brazilian recipient, time on dialysis, diabetic end-stage renal disease, retransplantation, preformed donor-specific anti-HLA antibodies, donor age, donor gender, donor diabetes, cerebrovascular death, donor final SCr, reversed cardiac arrest, vasoactive drugs, Eurocollins perfusion solution, machine perfusion, HLA mismatches, CIT, rabbit antithymocyte globulin induction, calcineurin-inhibitor-free regimen or introduction after 48h post-transplant, *de novo* mTOR inhibitor (full model available on Tables S1 and S2).

[a]This was the estimated rate ratio for a one-unit increase in the variable. – Each month on dialysis before the kidney transplant resulted in a 2% increase in days of DGF. – Each HLA mismatch resulted in an 8.3% increase in days of DGF. – Each 1 mg/dL in the donor final sCr resulted in a 6.4% increase in days of DGF. – Each hour of CIT resulted in a 2.3% increase in days of DGF.

[b]This was the estimated rate ratio when the dummy variable was 1 (yes). – Retransplants (compared to first transplants) were expected to have a 41.5% increase in the number of days of DGF. – Transplants with male donors (compared to female donors) were expected to have a 20.4% increase in the number of days of DGF. – Transplants in which rATG was used as induction therapy (compared to no induction or other induction drugs) were expected to have a 28.6% decrease in the number of days of DGF. – Transplants in which mTORi was used in the initial immunosuppressive regimen (compared to other strategies without *de novo* mTORi) were expected to have a 33% increase in the number of days of DGF.

#Generalized Linear Mixed Model with Logistic Regression, adjusted for Site/Center (random effect).

§Generalized Linear Mixed Model with Negative Binomial Regression, adjusted for Site/Center (random effect).

£Time on DGF (days) considering all analyzed sample (*n* = 2849) and attributing zero to patients who did not presented DGF: mean = 11.8, SD = 13.5, median = 2, IQR = 0–8. Time on DGF (days) considering only patients who presented DGF (*n* = 1446): mean = 6.0, SD = 11.2, median = 8, IQR = 4–14.

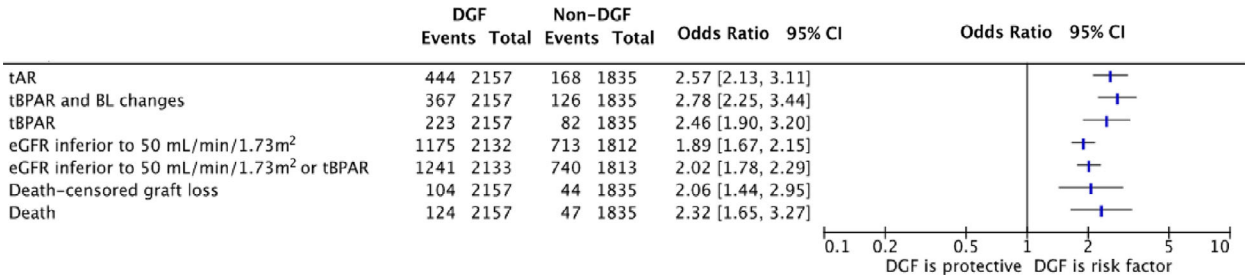

Figure 3 Association of DGF with transplant outcomes at 12 months, unadjusted analysis. AR: acute rejection; tBPAR: treated biopsy-proven acute rejection; BL: borderline; eGFR: estimated glomerular filtration rate.

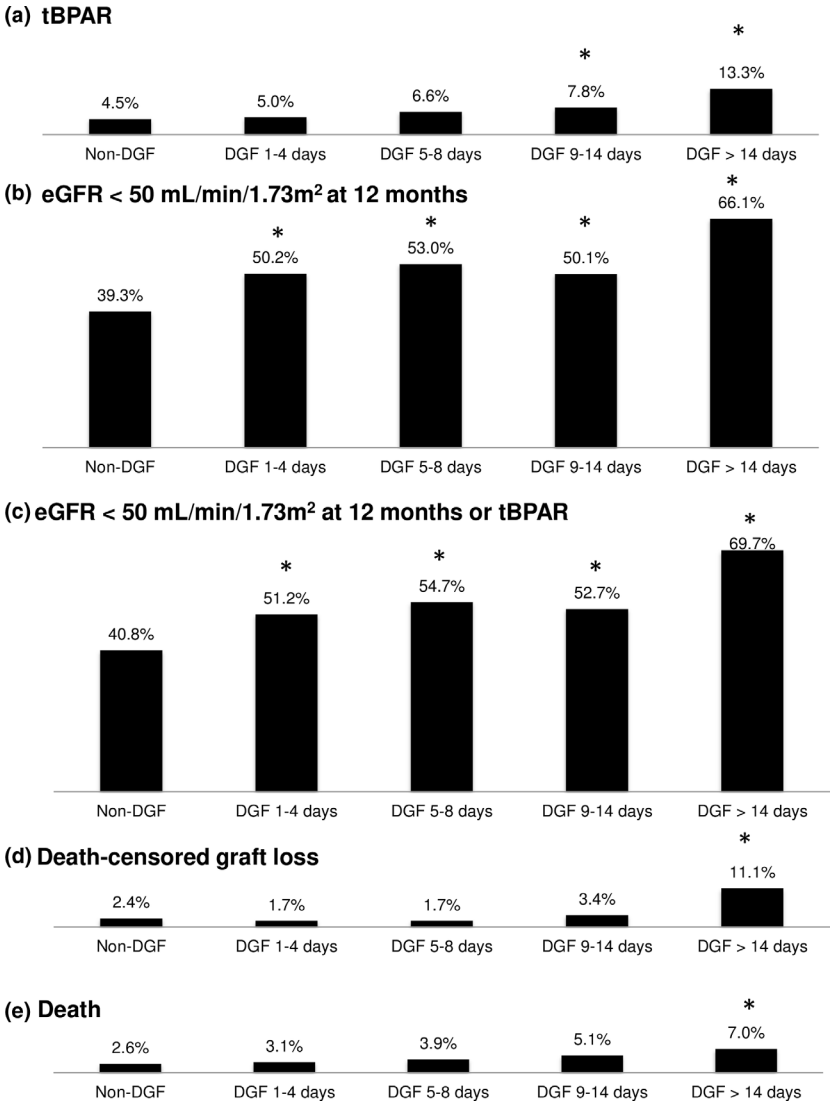

Figure 4 Transplant outcomes according to DGF quartiles. tBPAR: treated biopsy-proven acute rejection: eGFR: estimated glomerular filtration rate. *$P < 0.05$ vs. Non-DGF group.

analysis, we are not able to evaluate the magnitude of these concerns. The high CIT was notable and its contribution to DGF is unequivocal. The large territorial extension, the allocation model, predominantly based on HLA compatibility, and the absence of specific allocation policies for expanded criteria donors probably contribute to the long CIT in our country. There is plenty of evidence that machine perfusion is associated with DGF incidence, with an unclear impact on DGF duration [22,23]. The use of machine perfusion was not

Table 3. Multivariable analyses for the impact of time on DGF on transplant outcomes

	Quartiles of time on DGF				
	Non-DGF	DGF 1–4 days	DGF 5–8 days	DGF 9–14 days	DGF > 14 days
N	1856	483	483	474	443
tBPAR*	REF	$_{0.666}1.051_{1.659}$	$_{0.884}1.348_{2.056}$	$_{0.824}1.270_{1.957}$	$_{\mathbf{1.462}}\mathbf{2.145}_{\mathbf{3.147}}$
eGFR <50 ml/min/1.73m^2 at 12m†	REF	$_{0.911}1.163_{1.483}$	$_{\mathbf{1.104}}\mathbf{1.406}_{\mathbf{1.791}}$	$_{\mathbf{1.069}}\mathbf{1.365}_{\mathbf{1.743}}$	$_{\mathbf{1.865}}\mathbf{2.445}_{\mathbf{3.207}}$
eGFR <50 ml/min/1.73m^2 at 12m^2 or tBPAR*	REF	$_{0.929}1.170_{1.487}$	$_{\mathbf{1.152}}\mathbf{1.464}_{\mathbf{1.859}}$	$_{\mathbf{1.111}}\mathbf{1.414}_{\mathbf{1.799}}$	$_{\mathbf{2.250}}\mathbf{2.960}_{\mathbf{3.894}}$
Death-censored graft loss†	REF	$_{0.489}0.865_{1.528}$	$_{0.498}0.873_{1.527}$	$_{0.638}1.081_{1.831}$	$_{\mathbf{1.572}}\mathbf{2.409}_{\mathbf{3.691}}$
Death†	REF	$_{0.595}0.988_{1.641}$	$_{0.647}1.064_{1.750}$	$_{0.848}1.348_{2.144}$	$_{\mathbf{1.081}}\mathbf{1.713}_{\mathbf{2.712}}$

All analyses were performed using Generalized Linear Mixed Model with Logistic Regression, adjusted for Site/Center (random effect).

DGF, delayed graft function; tBPAR, treated biopsy-proven acute rejection; eGFR; estimated glomerular filtration rate; REF, reference.

*Variables included in the model: gender, recipient age, Afro-Brazilian recipient, time on dialysis, diabetes as end-stage renal disease cause, retransplantation, preformed donor-specific anti-HLA antibodies, donor age, donor gender, donor diabetes, cerebrovascular death, donor final sCr, HLA mismatches, rabbit antithymocyte globulin induction, calcineurin-inhibitor-free regimen or introduction after 48h posttransplant, *de novo* mTOR inhibitor, time on DGF (full model available on Table S4).

†Variables included in the model: gender, recipient age, Afro-Brazilian recipient, time on dialysis, diabetes as end-stage renal disease cause, retransplantation, preformed donor-specific anti-HLA antibodies, donor age, donor gender, donor diabetes, cerebrovascular death, donor final sCr, HLA mismatches, rabbit antithymocyte globulin induction, calcineurin-inhibitor-free regimen or introduction after 48h posttransplant, *de novo* mTOR inhibitor, time on DGF, treated biopsy-proven acute rejection (full model available on Table S4).

associated with a shorter duration of DGF in our cohort. rATG induction was associated with reduced incidence and duration of DGF. There is biologic plausibility to explain these findings, since rATG inhibits leukocyte migration and downregulates leukocyte adhesion molecules, potentially minimizing IRI [24]. This effect has been previously suggested in a unique single-center randomized clinical trial using rATG 3–6 mg/Kg intraoperatively, but these results were not replicated [25]. Unfortunately, we did not capture information on the timing of rATG infusion, dose, and clinical indication. In line with the recently published meta-analysis, *de novo* mTORi was associated with DGF duration but not with DGF occurrence [26].

The variation in the incidence of DGF among centers was remarkable. Brazil has continental dimensions and marked regional disparities. Main differences among centers are the State territorial extension, the State's donation performance, local policies of KT in sensitized patients and in patients with comorbid conditions, acceptance rates of "nonideal" organs; machine perfusion availability, and immunosuppression protocols. The sites with the lowest DGF rates were those with more favorable recipient clinical profile, donors with lower KDPI, shorter CIT and/or broader use of machine pulsatile perfusion (data not shown). However, these variables not immediately explain the incidence of DGF in centers with the highest rates, suggesting that other variables that were not accounted for in our analysis might participate in the pathophysiology of the DGF. A recent study observed that poor donor clinical and hemodynamic status was associated with the initial renal function [27]. Another indirect evidence is derived from a Brazilian study that reported high incidence of DGF among recipients of simultaneous pancreas–kidney transplants (22.7%), despite younger donors (25.6 ± 9.4 years old) and shorter CIT (14 ± 4 h) [28].

Evidence suggests that prolonged DGF is associated with an increased risk of acute rejection episodes and lower 1-year patient and graft survivals [8,29]. Yet, it is still debatable whether the association between DGF on inferior graft survival is independent of the concomitant presence of acute rejection. Our results demonstrated that DGF *per se* is associated with inferior graft function and survival as early as one year, emphasizing the theory of chronic kidney damage secondary to the maladaptive repair after ischemic acute tubular necrosis [30]. While only DGF longer than 14 days was associated with an increased incidence of acute rejection, and inferior patient and allograft survivals, we observed an association between increasing duration of DGF and decreasing

1-year renal function. Because 1-year renal function has been consistently associated with long-term graft survival [31], even shorter durations of DGF may be also associated with inferior long-term allograft survival.

As in any registry data analysis, our study has inherent limitations. The retrospective nature precludes definitive conclusions. Missing data may have influenced the outcomes of multivariable analyses. We were unable to capture detailed information on donor maintenance. Due to the lack of standardization, we were not able to critically assess the influence of immunosuppressive strategies on the incidence and duration of DGF. Finally, our analysis was restricted to short-term outcomes precluding any long-term conclusion.

In summary, this multicenter study with a large sample size, national representation, standardized definition of DGF and with robust center-adjusted analysis confirms the high incidence of DGF and its duration-dependent association with short-term outcomes. These data may support information to Brazilian transplant community and government entities to carry out strategies to minimize DGF, focusing on potentially modifiable risk factors, as those related to organ preservation. Longer CIT is probably the one of the most important factors impacting on DGF. Measures to shorten CIT include the following: specific allocation policies for ECD, reducing local discard and the need for organ export to another region; precise indication of procurement kidney biopsy; use of donor blood (instead of lymph nodes) for crossmatch; use of virtual crossmatch alone or as a preselection tool; and critical prescription of pretransplant hemodialysis [32]. Expanding the use of pulsatile machine perfusion would certainly be useful, but cost-effectiveness studies would be necessary to assess the feasibility. Finally, despite not directly assessed in this study, we strongly believe that measures to shorten the time between brain death and retrieval surgery and to improve donor maintenance are also necessary to reduce DGF rates in our setting.

Authorship

TS-F, MM, RM and HT-S: participated in research design, in the performance of the research, in the writing of the paper, and data analysis and analytic tools. LGA, AV and MdS: participated in the performance of the research, in the reviewing of the paper, and data analysis and analytic tools. JMP, VG, DC, RE, CO, DS, LD, ED-N, FC, APeSF, GF, RM, AB, GM, EPL, EK, TM, SC, HN, PF, HN, MAV, FA, IF, ACM, JB, SV, SH, AS and ML: participated in the performance of the research and in the writing/reviewing of the paper. CO, CF, RK, CF, MC, SS, CV, LA, ET, GO, MP, FM and LGA: participated in the performance of the research.

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Conflict of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Risk factors for DGF.

Table S2 Risk factors for time on DGF.

Table S3 Risk factors for 1-year outcomes.

Table S4 Risk factors for 1-year outcomes including quartiles of duration of DGF in the model.

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APPENDIX

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