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The effect of delayed graft function on graft and patient survival in kidney transplantation: an approach using competing events analysis

Isabel Fonseca,[1,2,3] Laetitia Teixeira,[4,3] Jorge Malheiro,[1,2] La Salete Martins,[1,2] Leonídio Dias,[1] António Castro Henriques[1,2] and Denisa Mendonça[4,3]

1 Department of Nephrology and Kidney Transplantation, Centro Hospitalar do Porto, Hospital de Santo António, Porto, Portugal
2 Unit for Multidisciplinary Investigation in Biomedicine (UMIB), Porto, Portugal
3 EPIUnit-Institute of Public Health, University of Porto, Porto, Portugal
4 Department of Population Studies, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal

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kidney transplantation, delayed graft function, competing risks analysis, long-term graft failure, patient death with graft function, subdistribution hazard regression model.

Correspondence
Isabel Fonseca, Department of Nephrology and Kidney Transplantation, Centro Hospitalar do Porto, Hospital de Santo António, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal.
Tel.: +351914740001;
fax: 223 320 318
e-mail: isabelf27@gmail.com

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The authors declare that they have no competing interests. The results presented in this study have not been published previously in whole or part, neither in abstract format.

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Abstract

Objective: In kidney transplantation, the impact of delayed graft function (DGF) on long-term graft and patient survival is controversial. We examined the impact of DGF on graft and recipient survival by accounting for the possibility that death with graft function may act as a competing risk for allograft failure.
Study design and Setting: We used data from 1281 adult primary deceased-donor kidney recipients whose allografts functioned at least 1 year.
Results: The probability of graft loss occurrence is overestimated using the complement of Kaplan–Meier estimates (1-KM). Both the cause-specific Cox proportional hazard regression model (standard Cox) and the subdistribution hazard regression model proposed by Fine and Gray showed that DGF was associated with shorter time to graft failure (csHR = 2.0, $P = 0.002$; sHR = 1.57, $P = 0.009$), independent of acute rejection (AR) and after adjusting for traditional factors associated with graft failure. Regarding patient survival, DGF was a predictor of patient death using the cause-specific Cox model (csHR = 1.57, $P = 0.029$) but not using the subdistribution model.
Conclusions: The probability of graft loss from competing end points should not be reported with the 1-KM. Application of a regression model for subdistribution hazard showed that, independent of AR, DGF has a detrimental effect on long-term graft survival, but not on patient survival.

Introduction

Delayed graft function (DGF) is the most common complication affecting kidney allografts in the immediate post-transplant period. The rate of DGF after kidney transplantation (KTx) can vary from 2% to 50% depending on the definition and the practice center, and it is one of the most important risk factors for both acute rejection (AR) and impaired renal function at one year [1–4].

The impact of DGF on long-term graft survival is controversial [4]. Some single-center studies have reported limited or no impact of DGF on long-term graft survival in the absence of AR [5–8] while others have associated DGF with poor graft outcome independent of rejection [9–12]. Some authors have examined the association between DGF and patient survival, also with conflicting findings. Some of those studies reported no association between DGF with patient death with a functioning graft [6, 13], whereas

others showed a negative effect of DGF on survival of KTx recipients [9, 14–17].

Survival analysis is used to analyze time-to-event data and is commonly used in medical research [18]. In KTx, the Kaplan–Meier curves are one of the most used methodologies to study graft and patient survival, which censor all but one type of outcome. However, a patient can be at risk for more than one type of events and experience an event different from the outcome of interest. For example, when analyzing kidney allograft survival, the event of interest is chronic graft loss, but other events can be observed, namely patient death with graft function. These two events are termed competing risk events. That is, a competing risk is an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters the probability of occurrence of this other event [19, 20]. If a recipient dies, the decline and loss of graft function cannot be observed. Graft failure and patient death are competing end points that are mutually exclusive. Thus, appropriate methods accounting for the presence of competing risk events must be applied in the analysis and interpretation of such data.

Inappropriate methods such as the complement of Kaplan–Meier estimate (1-KM) have been applied to estimate probabilities of the occurrence of an event of interest in a competing risks setting [21] [19, 21–23]. This method produces biased estimates of end point probabilities because does not account for the various types of potential outcomes [20, 24]. In other words, the probability of an event of interest (e.g., graft failure) is estimated in an ideal world in which the other types of events do not exist (patient death, for example). Thus, when competing risks are present, cumulative incidence function (CIF) is the appropriate tool to analyse such data [22, 25]. Cumulative incidence function for a specific event, also known as the subdistribution function, is defined as the probability of failing from a given cause in the presence of competing events, given that a subject has survived or has already failed from different causes [20, 26, 27]. In other words, the cumulative incidence denotes the expected proportion of patients with a certain event over the course of time [22].

In the competing risks context and depending on the purpose of the study, there are different methods to quantify the effect of a covariate [22, 23]. The most common methods are the regression on cause-specific hazards using the competing risks analog to the Cox proportional hazards model, and the regression model for the cumulative incidence function proposed by Fine and Gray [26]. This method is based on the hazard of the subdistribution, providing a simple relationship between covariates and CIF, and is recommended for a competing risk approach [20, 26, 28]. As in any other regression analysis, modeling CIF can be used to identify potential prognostic factors for a particular failure in the presence of competing risks or to assess a prognostic factor of interest after adjusting for other potential risk factors in the model [27].

The kidney transplant program at our center began in 1983. From that time to the present, the rates of DGF varied due to the distinctive immunosuppressive protocols introduced, the inclusion of kidneys from living donors, and more recently the inclusion of expanded-criteria donors (ECD). We reviewed our KTx experience over the past three decades to study what effect evolving DGF (with and without AR associated) had on patient and long-term kidney transplant outcomes. Our analysis further supplements the current state of knowledge by assessing the impact of DGF on graft and recipient survival and by accounting for the possibility that death with graft function may act as a competing risk for allograft failure.

Materials and methods

Subjects and study design

This retrospective single-center study used data from the renal transplant database of the Department of Nephrology and Kidney Transplantation of Centro Hospitalar do Porto. Analyses were conducted on data from adult recipients who received a primary deceased-donor kidney transplant from August 1983 through December 2012 at this center and had a functioning renal allograft for at least 1 year. Exclusion criteria were (i) patients younger than 18 years old ($n = 144$), (ii) multi-organ transplant recipients, including kidney–pancreas ($n = 169$), (iii) retransplants ($n = 163$), (iv) recipients of living kidney donor ($n = 150$), and (v) recipients whose allografts functioned <1 year ($n = 196$). Patients with missing data on DGF or AR were also excluded from the analysis ($n = 33$, 2.5% of the final cohort). Because organ donation after circulatory death is not performed in our country, all donations occurred after brain death.

All patients were followed up from the time of transplant until death, graft failure or until December 31, 2013. The study was approved for the Institutional Review Board of Centro Hospitalar do Porto.

Definitions, variable categorization and main outcomes

The primary exposure of interest was the development of DGF after transplantation, with or without AR. In the current study, DGF was defined as the need for dialysis during the first week after transplantation. This definition was the same over the observation period of the three decades. Acute rejection was defined as either biopsy-proven rejection or antirejection treatment without biopsy. A variable "DGF-AR" was created with four categories: neither DGF nor AR; only DGF; only AR; DGF and AR. The cause of

kidney disease was categorized into three groups representing glomerular disease, diabetes, and all other diseases.

The study sample was divided into four cohorts based on the times in which immunosuppressive medications were introduced into clinical practice ("Transplant Era"): "Era" *1*, before 1990, the time of azathioprine and cyclosporine, no microemulsion; "Era" 2, between 1990 and 1995, the era of cyclosporine microemulsion; "*Era*" 3, between 1996 and 2000, marked by mycophenolate mofetil introduction and by the wide use of antithymocyte globulin; and "Era" 4, after 2000, the time of sirolimus availability and wide use of tacrolimus.

Time on dialysis prior to transplant was categorized as $<$ and $\geq$5 years. Peak panel reactive antibody level (PRA-peak) was categorized into two categories according to the cutoff of 10%.

"Female-donor mismatch" was labeled when a male recipient received a kidney from a female donor. Patients were grouped as female donor to male recipient or all other combinations (female to female, male to male, or male to female).

The difference between donor and recipient age (recipient age subtracted from donor age) was divided into four groups, each representing approximately 25% of the patients according to quartiles (1stQ: <-15 years; 2ndQ: ≥-15 and ≤-4 years; 3rdQ: >-4 and $\leq+6$ years; 4thQ: $>+6$ years). Donors over the age of 60 or donors over the age of 50 with two of the following were classified as ECD: history of high blood pressure, serum creatinine $\geq$1.5 mg/dl, or death resulting from a stroke.

Graft loss was defined as the absence of kidney function occurring any time after transplantation due to either patient death with a functioning allograft ("patient death") or irreversible graft injury requiring chronic dialysis and/or retransplantation ("graft failure").

Statistical analyses

Descriptives of baseline characteristics that were identified by univariate survival analysis (unadjusted) or traditionally considered as potential confounders for graft loss were calculated, and the results are shown across DGF-AR groups (Table 1). The following potential confounders were examined in unadjusted and adjusted multivariable models: (i) recipient factors (age, cause of ESRD, PRA-peak, time on dialysis prior to transplant, HCV infection status); (ii) donor factors (ECD versus standard deceased-donor); and (iii) transplant factors (number of HLA mismatches, donor-age difference, "female-donor mismatch", and Transplant Era). Continuous variables are expressed as the mean and standard deviation (SD), and categorical variables are expressed as proportions.

Survival analysis was performed for analyzing graft and patient survival. To analyze graft survival, the event of interest was graft failure and the competing risk event was patient death with graft function. To analyze patient survival, the event of interest was patient death with graft function and the competing end point was graft failure. Patients without any of these outcomes were censored at the date of their last recorded visit or at the end of the study period (December 2013).

First, estimates of CIF taking competing risks into account were calculated and compared with the (1-km) estimates. Second, regression models taking competing risks into account were carried out to analyze the effect of covariates in the graft and in the patient survival. This analysis was performed considering two types of hazard: cause-specific hazard and subdistribution hazard. Proportional cause-specific hazard regression models were performed using the standard Cox cause-specific hazard regression model, censoring all patients without the event of interest. An alternative model proposed by Fine and Gray [26] was the approach used in the current study to model the subdistribution hazard.

An exploratory analysis was performed to examine the unadjusted effect of the traditional potential confounders by fitting univariable models. The cause-specific hazard ratio (csHR) and the subdistribution hazard ratio (sHR) for graft loss either due to declining function or to patient death according to the primary exposure of interest (DGF-AR) were estimated in a multivariable analysis adjusting for the influence of these potential confounders. The group of categorical variables with lower proportion of the end point (graft failure or patient death) was considered as the reference class. Therefore, the 1st and the 4th quartiles of donor-age difference were considered the reference classes in graft and patient survival, respectively.

As the main objective of this study was to assess the prognostic value of a specific variable of interest (DGF-AR), we opted to study the impact of DGF-AR in graft and patient survival after adjusting for other risk factors traditionally considered as potential confounders in the model, even those that were nonsignificant. The impact of DGF-AR on graft and patient survival was similar when including in the model only the statistical significant variables (supplemental data).

About 37.4% (n = 479) of patients had at least one variable missing. The main variable of interest DGF-AR and the survival outcome (patient death and graft failure) presented no missing values. Missing data were considered to be missing completely at random. Therefore, missing data were dealt by carrying complete case analyses, in which patients were excluded in multivariable analyses if the required variables were missing.

Statistical analyses were performed using SPSS version 22.0 (IBM SPSS Statistics, IBM Corporation, Chicago,

Table 1. Patient demographic and clinical characteristics by DGF-AR occurrence (n = 1281).

Characteristic	No DGF nor AR (n = 721)	DGF only (n = 274)	AR only (n = 175)	DGF + AR (n = 111)
Recipient				
Age (yr), mean (SD)	43.8 (12.3)	46.0 (12.3)	36.8 (12.2)	39.8 (12.4)
Gender				
Male	427 (54.9)	175 (22.5)	111 (14.3)	65 (8.4)
Female	294 (58.4)	99 (19.7)	64 (12.7)	46 (9.1)
Cause of ESRD (*n*, %)				
Glomerulonephritis	274 (57.7)	96 (20.2)	69 (14.5)	36 (7.6)
Diabetes	40 (56.3)	18 (25.4)	5 (7.0)	8 (11.3)
Other	407 (55.4)	160 (21.8)	101 (13.7)	67 (9.1)
Peak PRA (*n*, %)				
<10	533 (60.4)	1784 (20.8)	99 (11.2)	67 (7.6)
≥10	92 (45.8)	50 (24.9)	34 (16.9)	25 (12.4)
Unknown/missing	96 (48.7)	40 (20.3)	42 (21.3)	19 (9.6)
Time on dialysis (mo)				
Mean (SD)	3.9 (3.6)	4.2 (3.4)	3.3 (3.1)	4.0 (3.5)
≥ 5 years (*n*, %)	198 (57.6)	78 (22.7)	35 (10.2)	33 (9.6)
Unknown/missing	31 (57.4)	17 (31.5)	4 (7.4)	2 (3.7)
HCV infection (*n*, %)				
HCV-negative	608 (56.6)	229 (21.3)	151 (14.1)	86 (8.0)
HCV-positive	58 (48.3)	36 (30.0)	12 (10.0)	14 (11.7)
Unknown/missing	55 (63.2)	9 (10.3)	12 (13.8)	11 (12.6)
Donor				
Age (yr), mean (SD)	37.7 (14.5)	39.9 (14.9)	36.0 (12.9)	37.3 (12.4)
ECD (*n*, %)	84 (49.4)	55 (32.4)	18 (10.6)	13 (7.6)
Unknown/missing	9 (69.2)	2 (15.4)	1 (7.7)	1 (7.7)
Donor-Recipient				
Cold ischemia time (h)				
Mean (SD)	22.2 (8.6)	23.9 (4.9)	22.8 (4.1)	24.0 (4.6)
Unknown/missing (*n*, %)	389 (65.2)	107 (17.9)	63 (10.6)	38 (6.4)
HLA mismatches				
A	1.23 (0.67)	1.17 (0.70)	1.22 (0.63)	1.22 (0.61)
Unknown/missing	42 (64.6)	11 (16.9)	11 (16.9)	1 (1.5)
B	1.21 (0.68)	1.24 (0.67)	1.35 (0.67)	1.29 (0.71)
Unknown/missing	39 (61.9)	12 (19.0)	11 (17.4)	1 (1.6)
DR	0.68 (0.69)	0.61 (0.66)	0.74 (0.73)	0.63 (0.64)
Unknown/missing	35 (54.7)	13 (20.3)	12 (18.8)	4 (6.3)
Female-donor mismatch				
Yes	82 (33.2)	50 (20.2)	21 (8.5)	94 (38.1)
No	523 (61.4)	186 (21.8)	133 (15.6)	10 (1.2)
Unknown/missing	116 (63.7)	38 (20.9)	21 (11.5)	7 (3.8)
Donor-recipient age difference (*n*, %)				
≤ −15 yr than recipient	183 (61.4)	67 (22.5)	31 (10.4)	17 (5.7)
−15.1 to −4 yr than recipient	162 (54.4)	69 (23.2)	39 (13.1)	28 (9.4)
−4.1 to +6 yr than recipient	157 (52.7)	59 (19.8)	49 (16.4)	33 (11.1)
> + 6 yr than recipient	150 (52.1)	57 (19.8)	50 (17.4)	31 (10.8)
Unknown/missing (*n*, %)	69 (77.5)	12 (13.5)	6 (6.7)	2 (2.2)
Transplantation Era				
1983–1990	46 (29.5)	31 (19.9)	39 (25.0)	40 (25.6)
1990–1995	152 (49.4)	70 (22.7)	58 (18.8)	28 (9.1)
1996–2000	150 (55.8)	62 (23.0)	41 (15.2)	16 (5.9)
2001–2012	371 (69.2)	104 (19.4)	37 (6.9)	24 (4.5)

Percentages are calculated within DGF-AR status. ERSD, end-stage renal disease; ECD, expanded-criteria donors; HCV, Hepatitis C virus; SD, standard deviation; yr, year. No missing values for the variables: recipient age and gender, cause of ERSD, and transplantation era.

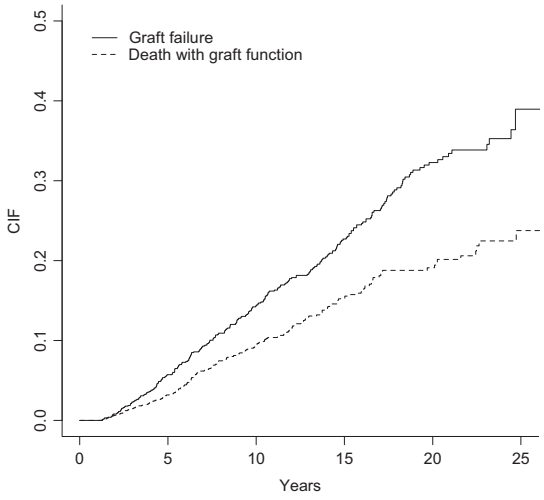


Figure 1 Cumulative incidence curves for all possible outcomes taking competing risks into account. CIF, Cumulative incidence function.

IL, USA) and R software using the packages *coxph* and *cmprsk*. A significance level of 0.05 was considered.

Results

Sample

The final sample included 1281 primary adult kidney recipients transplanted between 1983 and 2012. About 60.7% were male, and the overall mean age was 43.0 years (SD = 12.6). Median follow-up was 9.8 years (range 1.0–30.2 years). A total of 424 (33.1%) grafts were lost during the study period, either as a result of loss of function (n = 258, 60.8%) or patient death (n = 166, 39.2%). The main causes of patient death with graft function were cardiovascular disease (n = 63, 38.0%), followed by malignancies (n = 35, 21.1%) and infection (n = 26, 15.7%).

Cumulative incidence function

Figure 1 summarizes the cumulative incidence estimates for the two possible outcomes taking competing risks into accounts (the survival plots were halted at 25 years because the proportion of patients free of an event, but still in follow-up, becomes small). The probabilities of experiencing graft failure by 5, 10, and 20 years after KTx were 0.06, 0.14, and 0.32, respectively. The probabilities of death with graft function were 0.03, 0.09, and 0.19, respectively.

Cumulative incidence estimates versus the complement of Kaplan–Meier estimates

Figure 2 presents the curves for the CIF of the occurrence of the event of interest obtained using two different methods: taking competing risks into account and the 1-KM.

The appropriate competing risks approach to estimate CIF results in a lower estimate of cumulative incidence. The magnitude of the difference in the incidence of graft

Figure 2 The complement of the Kaplan–Meier estimate and the cumulative incidence estimate for graft failure and death with graft function. CR, competing risks; 1-KM, Complement of Kaplan–Meier estimate.

failure and patient death, as calculated using the two methods, increases with the period of follow-up, mainly after the tenth year. In other words, the actual probabilities of graft failure and patient death are overestimated using the Kaplan–Meier method. Furthermore, the longer the duration of follow-up is the larger the difference between the estimates by these two methods.

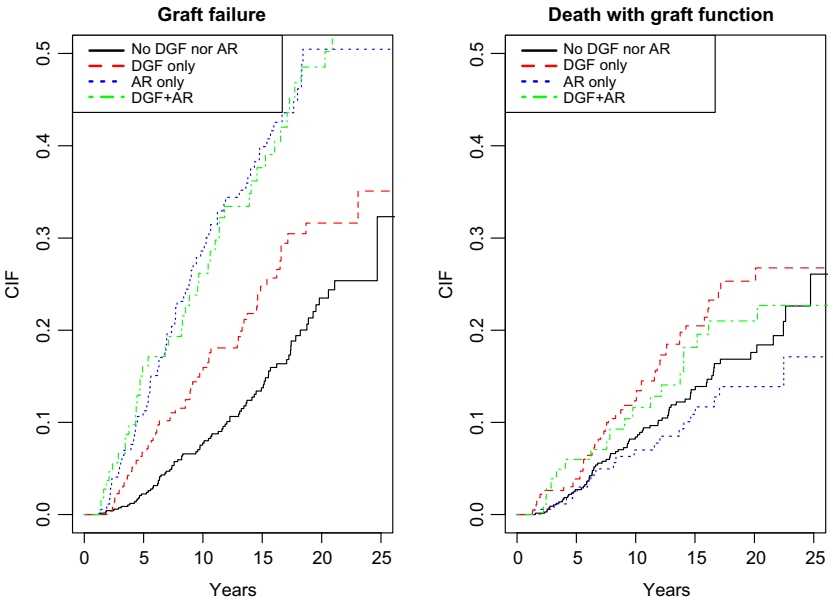
Delayed graft function and acute rejection

The overall incidence of DGF was 30.1% (385 grafts) and was not associated with AR in 274 grafts (21.4%) and was associated with AR in 111 (8.7%). The overall occurrence of DGF declined over decades from 45.5% in Era 1 to 31.8% in Era 2, 29.0% in Era 3, and 23.9% in Era 4. The overall incidence of AR similarly decreased from 50.6% in Era 1 to 27.9% in Era 2, 21.2% in Era 3, 11.4% in Era 4. The characteristics of the recipients according to DGF-AR status are summarized in Table 1.

The Fig. 3 displays the cumulative incidence curves for graft failure and death with graft function according to DGF-AR status. Differences were found between DGF-AR status with regard to the graft failure: all three categories of the variable DGF-AR (DGF only, AR only, and both DGF and AR) had a higher probability of graft failure than the non-DGF/non-AR category. Concerning patient survival, the differences between DGF-AR groups were not so pronounced.

The impact of DGF on graft and patient survival by Cox and Fine and Gray regression models

Tables 2 and 3 give a summary of the unadjusted and adjusted effects of covariates for graft failure and patient death with graft function based on the two types of models: the cause-specific hazard model (standard Cox proportional hazards regression) and the subdistribution hazard model (Fine and Gray model).



Number at risk at: (years)	0	5	10	15	20	25
Graft failure						
No DGF nor AR	721	555	392	268	148	88
DGF	274	221	166	115	78	55
AR	175	144	101	76	39	25
DGF + AR	111	80	63	47	36	23
Patient Death						
No DGF nor AR	721	552	388	267	157	96
DGF	274	228	173	123	88	65
AR	175	159	135	120	89	74
DGF + AR	111	90	77	65	59	49

Figure 3 Cumulative incidence curves for graft failure and death with graft function according to DGF-AR status. DGF, Delayed graft function; AR, acute rejection.

Table 2. Cox proportional hazard regression (cause-specific hazard model) for all possible events.

		Unadjusted models			Adjusted model (n = 802)		
		csHR	95% CI	*P* value	csHR	95% CI	*P* value
Graft Failure (censored for patient death)	**DGF-AR** (reference: non-DGF and non-AR)						
	Only DGF	1.79	1.28–2.48	0.001	2.00	1.30–3.07	0.002
	Only AR	2.99	2.17–4.10	<0.001	2.81	1.81–4.38	<0.001
	DGF + AR	3.37	2.35–4.84	<0.001	2.60	1.58–4.27	<0.001
	Transplant Era (reference: Era 4 > 2000)						
	Era 1 (<1990)	2.58	1.65–4.03	<0.001	3.21	1.47–7.04	0.004
	Era 2 (1990–1995)	2.03	0.34–3.09	0.001	3.64	1.73–7.62	0.001
	Era 3 (1996–2000)	0.92	0.57–1.49	0.74	1.66	0.78–3.55	0.19
	ECD (yes vs. no)	2.41	1.73–3.34	<0.001	2.49	1.35–4.60	0.003
	Donor-recipient age difference (reference: 1st Q: < - 15 yr)						
	2nd Q (≥−15 and ≤ −4 yr)	1.76	1.16–2.69	0.009	1.60	0.89–2.88	0.12
	3rd Q (> - 4 and ≤ +6 yr)	2.35	1.56–3.53	<0.001	1.73	0.94–3.21	0.081
	4th Q (> + 6 yr)	3.91	2.66–5.77	<0.001	2.62	1.32–5.20	0.006
	Cause of ESRD (reference: others)						
	Diabetic nephropathy	1.71	1.01–2.89	0.046	1.21	0.47–3.12	0.069
	Glomerulonephritis	1.12	0.87–1.45	0.38	0.75	0.75–1.47	0.77
	Time on dialysis (>5 vs. <5 yr)	1.24	0.93–1.65	0.14	1.42	0.97–2.06	0.13
	Peak PRA (>10 vs. <10)	1.26	0.92–1.73	0.15	0.93	0.63–1.35	0.69
	HCV infection (positive vs. negative)	1.43	1.02–2.00	0.039	1.12	0.73–1.70	0.61
	Female-donor mismatch (yes vs. no)	0.98	0.68–1.44	0.98	0.84	0.50–1.41	0.51
	HLA MM A (reference: 0)						
	1 vs. 0	1.18	0.80–1.74	0.19	1.19	0.71–1.97	0.51
	2 vs. 0	1.24	0.82–1.89	0.17	1.21	0.70–2.11	0.50
	HLA MM B (reference: 0)						
	1 vs. 0	1.04	0.71–1.52	0.77	1.16	0.71–1.92	0.55
	2 vs. 0	1.12	0.75–1.67	0.57	1.46	0.87–2.47	0.16
	HLA MM DR (reference: 0)						
	1 vs. 0	1.02	0.79–1.33	0.75	1.00	0.72–1.41	0.97
	2 vs. 0	0.65	0.36–1.15	0.11	0.74	0.34–1.59	0.44
	Recipient age (1-yr increase)	0.97	0.96–0.98	<0.001	0.99	0.97–1.01	0.27

Graft survival

The variables identified as significant predictors of graft failure in unadjusted cause-specific hazard models, and unadjusted Fine and Gray models were similar (Tables 2 and 3). In both statistical approaches, all three categories of the variable DGF-AR (DGF only, AR only, and both DGF and AR) had a deleterious effect on graft survival compared to the neither DGF nor AR category. The other covariates associated with graft failure were the Transplant Eras (Eras 1 and 2 vs. 4), grafts from ECD, donor-recipient age difference (2nd, 3rd, and 4th quartiles vs. 1st quartile), cause of ERSD (diabetes vs. other), positive HCV status (nearly reaching the significance level in Fine and Gray model) and recipient age.

In multivariable models (Tables 2 and 3, cause-specific and subdistribution hazard models, respectively), DGF with or without AR as well as AR only remained consistently associated with graft failure. Furthermore, recipients whose cause of ERSD was diabetes (nearly reaching the significance level in the cause-specific hazard model), transplantation in Eras 1 and 2, kidneys from ECD or from donors with an age difference of more than 6 years, were also associated with poor graft survival. In both models, when the donor-recipient age difference was added, the recipient's age became nonsignificant.

Patient survival

In relation to patient death with graft function, in the unadjusted cause-specific hazard models and unadjusted Fine and Gray models, the predictors of patient survival were slightly different among models (Tables 2 and 3). In the unadjusted cause-specific hazard models, the variables DGF (isolated or associated to AR), Transplant Era, ECD, donor-recipient age difference, cause of ERSD, pretransplant time on dialysis, PRA-peak, HCV status, and recipient age were significantly associated with patient death (Table 3). In the unadjusted Fine and Gray model, however, the variables identified as predictors of patient

Table 2. continued

		Unadjusted models			Adjusted model (n = 802)		
		csHR	95% CI	*P* value	csHR	95% CI	*P* value
Patient Death (censored for graft failure)	**DGF-AR** (reference: non-DGF and non-AR)						
	Only DGF	1.95	1.41–2.68	<0.001	1.57	1.05–2.35	0.029
	Only AR	1.29	0.85–1.95	0.23	1.19	0.69–2.03	0.54
	DGF + AR	2.36	1.57–3.54	<0.001	1.34	0.76–2.34	0.31
	Transplant Era (reference: Era 4 > 2000)						
	Era 1 (< 1990)	2.63	1.69–4.08	<0.001	5.29	2.59–10.8	<0.001
	Era 2 (1990–1995)	1.39	0.90–2.14	0.139	3.11	1.58–6.12	0.001
	Era 3 (1996–2000)	0.73	0.45–1.20	0.214	1.12	0.56–2.23	0.76
	ECD (yes vs. no)	1.58	1.05–2.37	0.027	0.82	0.39–1.70	0.59
	Donor-recipient age difference (reference: 4th Q: > +6 yr)						
	1st Q (<−15 yr)	1.54	1.04–2.28	0.03	0.55	0.28–1.11	0.55
	2rd Q (≥−15 and ≤ −4 yr)	1.10	0.72–1.68	0.65	0.70	0.38–1.31	0.70
	3rd Q (> - 4 and ≤ +6 yr)	1.14	0.74–1.74	0.56	0.79	0.45–1.38	0.79
	Cause of ESRD (reference: others)						
	Diabetic nephropathy	2.56	1.60–4.11	<0.001	4.07	2.03–8.18	<0.001
	Glomerulonephritis	0.76	0.57–1.02	0.071	0.90	0.62–1.32	0.60
	Time on dialysis (>5 vs. <5 yr)	1.71	1.28–2.29	<0.001	1.49	1.01–2.20	0.048
	Peak PRA (>10 vs. <10)	1.46	1.06–2.01	0.021	1.29	0.89–1.86	0.18
	HCV infection (positive vs. negative)	1.87	1.32–2.65	<0.001	1.56	1.00–2.41	0.048
	Female-donor mismatch (yes vs. no)	1.06	0.72–1.58	0.76	1.27	0.80–2.04	0.31
	HLA MM A (reference: 0)						
	1 vs. 0	0.75	0.51–1.10	0.15	0.86	0.53–1.39	0.53
	2 vs. 0	0.83	0.55–1.25	0.32	1.17	0.69–1.98	0.56
	HLA MM B (reference: 0)						
	1 vs. 0	1.27	0.82–1.98	0.47	1.19	0.69–2.03	0.54
	2 vs. 0	1.37	0.86–2.17	0.58	1.40	0.81–2.41	0.23
	HLA MM DR (reference: 0)						
	1 vs. 0	1.08	0.81–1.45	0.67	0.95	0.66–1.37	0.78
	2 vs. 0	1.22	0.74–2.00	0.07	1.18	0.65–2.14	0.59
	Recipient age (1-yr increase)	1.04	1.02–1.05	<0.001	1.05	1.03–1.08	<0.001

csHR, cause-specific hazard ratio; ERSD, end-stage renal disease; ECD, expanded-criteria donors; HCV, Hepatitis C virus; PRA, panel reactive antibody; HLA MM, HLA mismatches; yr, year; Q, quartile. The bold printed covariables indicate statistical significance in the multivariable model.

survival were as follows: DGF (DGF only vs. non-DGF/non-AR), Transplant Eras (Eras 1 and 2 vs. Era 4), donor-recipient age difference (1st, 2nd, and 3rd quartiles vs. 4th quartile), cause of ERSD (glomerulonephritis, associated with decreased HR), time on dialysis, PRA-peak, and recipient age.

Considering the multivariable regression models, the cause-specific hazard model showed that DGF only, Transplant Eras 1 and 2, diabetes as the cause of ESRD, pretransplant time on dialysis ≥5 years, positive HCV status and increasing recipient age had a deleterious effect on patient survival (Table 3). In the Fine and Gray adjusted model, only recipient age and Transplant Eras 1 and 2 were significantly associated with patient death (Table 4). In both models, Transplant Era (Era 2 vs. Era 4) emerged as significant when adjusted for any of the other variables included.

Unlike the adjusted cause-specific hazard model, the adjusted Fine and Gray model found that DGF was not significantly associated with patient death (csHR = 1.57, 95% CI = 1.05–2.35, P = 0.029 vs. sHR = 1.22, 95% CI = 0.85–1.76, P = 0.28). These differences are related to the different composition of the risk sets (in contrast to the cause-specific model where the DGF recipients who lost their graft were censored and removed from the risk set, in the subdistribution model, these same patients are maintained in the risk set) and to the increased risk of graft failure found for the recipients with DGF (these recipients had a 57% higher hazard risk of graft failure compared to non-DGF/non-AR: sHR = 1.57 95% CI = 1.12–2.21, P = 0.009).

Discussion

In this study, application of a regression model for subdistribution hazard showed that DGF, alone and independent of AR, has a significant detrimental effect on long-term graft survival but not on patient survival. Despite the

Table 3. Fine and Gray model (hazard of the subdistribution model) for all possible events.

		Unadjusted models			Adjusted model (n = 802)		
		sHR	95% CI	*P* value	sHR	95% CI	*P* value
Graft Failure	**DGF-AR** (reference: non-DGF and non-AR)						
	Only DGF	1.69	1.21–2.35	0.002	1.57	1.12–2.21	0.009
	Only AR	3.09	2.24–4.27	<0.001	2.57	1.85–3.56	<0.001
	DGF + AR	3.26	2.28–4.67	<0.001	2.26	1.52–3.37	<0.001
	Transplant Era (reference: Era 4 > 2000)						
	Era 1 (< 1990)	2.69	1.74–4.18	<0.001	1.87	1.11–3.14	0.019
	Era 2 (1990–1995)	2.23	1.49–3.33	0.001	1.93	1.23–3.03	0.004
	Era 3 (1996–2000)	1.02	0.64–1.65	0.93	0.96	0.58–1.60	0.88
	ECD (yes vs. no)	2.10	1.51–2.92	<0.001	1.73	1.09–2.74	0.019
	Donor-recipient age difference (reference: 1st Q: < −15 yr)						
	2nd Q (≥−15 and ≤ −4 yr)	1.82	1.20–2.76	0.005	1.56	0.97–2.50	0.066
	3rd Q (>−4 and ≤ +6 yr)	2.36	1.60–3.50	<0.001	1.65	1.01–2.70	0.049
	4th Q (> + 6 yr)	4.06	2.79–5.90	<0.001	2.52	1.44–4.41	0.001
	Cause of ESRD (reference: others)						
	Diabetic nephropathy	1.71	1.01–2.89	0.046	2.23	1.27–3.92	0.005
	Glomerulonephritis	1.12	0.87–1.45	0.38	1.08	0.83–1.41	0.57
	Time on dialysis (≥5 vs. <5 yr)	1.13	0.86–1.49	0.39	1.27	0.93–1.73	0.13
	Peak PRA (>10 vs. <10)	1.16	0.86–1.56	0.34	1.00	0.70–1.42	0.99
	HCV infection (positive vs. negative)	1.38	0.99–1.91	0.058	1.27	0.88–1.84	0.21
	Female-donor mismatch (yes vs. no)	0.96	0.66–1.42	0.85	1.02	0.69–1.49	0.94
	HLA MM A (reference: 0)						
	1 vs. 0	1.29	0.89–1.87	0.19	1.00	0.69–1.45	1.00
	2 vs. 0	1.33	0.89–1.99	0.17	1.12	0.75–1.68	0.57
	HLA MM B (reference: 0)						
	1 vs. 0	1.05	0.74–1.51	0.77	1.08	0.73–1.59	0.71
	2 vs. 0	1.12	0.76–1.63	0.57	1.31	0.88–1.96	0.19
	HLA MM DR (reference: 0)						
	1 vs. 0	1.04	0.81–1.35	0.75	1.08	0.82–1.43	0.57
	2 vs. 0	0.64	0.37–1.11	0.11	0.80	0.47–1.37	0.42
	Recipient age (1-yr increase)	0.97	0.96–0.98	<0.001	0.99	0.97–1.01	0.20

common use in clinical cancer research, the estimation of CIF and the application of competing risks models in nephrology is relatively recent [23, 29–38]. To the best of our knowledge, this is the first study that used a competing risks approach to address the impact of DGF on graft and patient survival.

Some previous studies have suggested that DGF without AR may have no impact on long-term graft survival [5–8]. Consistent with other reports [9–11], using both of the statistical approaches, our findings support that DGF per se is an independent predictor of graft failure. In fact, after adjusting for most of the factors traditionally associated with graft failure, early kidney dysfunction has a clear adverse effect on long-term graft survival meaning that the presence or absence of DGF will give an indication of the life expectancy of the kidney graft.

In addition to the DGF-AR status, the other factors independently associated with graft failure were, as expected, Transplant Eras 1 and 2, grafts from ECD donors, diabetes as a cause of ERSD and increasing donor-recipient age difference. Compared to donors who were more than 15 years younger than their recipients, all other categories showed a trend toward an increased risk of graft failure, including the category of donors who were 4–15 years younger than the recipient, with a near significant hazard of failure by the subdistribution approach. This finding was somewhat unexpected. The donor-recipient age difference was studied mostly in recipients from living donors. Grafts donated by live donors who were significantly older than recipients had similar graft and patient survival compared to recipients who received organs of a similar vintage [29, 39]. Shin *et al.* [40] evaluated whether the effect of donor age was different according to recipient age (≤−21, −20 to −1, 0–20, and ≥ 21 years) in kidneys from deceased donors. The authors confirmed that a negative donor-recipient age difference (recipients receiving kidneys from a donor younger than the recipient) was associated with greater death-censored graft survival. Our findings are in the line with this study. However, we did not expect that the narrow difference of donor-recipient age that we

Table 3. continued

		Unadjusted models			Adjusted model (n = 802)		
		sHR	95% CI	*P* value	sHR	95% CI	*P* value
Patient	DGF-AR (reference: non-DGF and non-AR)						
Death	Only DGF	1.53	1.08–2.19	0.018	1.22	0.85–1.76	0.28
	Only AR	0.80	0.49–1.30	0.370	0.84	0.50–1.41	0.51
	DGF + AR	1.29	0.78–2.15	0.320	1.10	0.63–1.93	0.74
	Transplant Era (reference: Era 4 > 2000)						
	Era 1 (< 1990)	1.80	1.09–2.95	0.021	3.74	2.00–7.02	<0.001
	Era 2 (1990–1995)	1.29	0.81–2.04	0.280	2.13	1.25–3.62	0.005
	Era 3 (1996–2000)	0.75	0.44–1.27	0.280	1.03	0.59–1.78	0.93
	ECD (yes vs. no)	1.14	0.70–1.85	0.60	0.88	0.49–1.71	0.70
	Donor-recipient age difference (reference: 4th Q: > +6 yr)						
	1st Q (<−15 yr)	3.07	1.90–4.95	<0.001	1.20	0.65–2.20	0.57
	2rd Q (≥−15 and ≤ −4 yr)	1.71	1.01–2.88	0.044	1.19	0.68–2.08	0.56
	3rd Q (>−4 and ≤ +6 yr)	1.82	1.07–3.10	0.027	1.54	0.90–2.65	0.12
	Cause of ESRD (reference: others)						
	Diabetic nephropathy	1.41	0.75–2.64	0.28	1.84	0.97–3.49	0.064
	Glomerulonephritis	0.62	0.44–0.88	0.007	0.76	0.54–1.07	0.12
	Time on dialysis (≥ 5 vs. <5 yr)	1.62	1.17–2.24	0.004	1.24	0.86–1.78	0.25
	Peak PRA (>10 vs. <10)	1.61	1.14–2.27	0.007	1.29	0.89–1.86	0.18
	HCV infection (positive vs. negative)	1.39	0.92–2.11	0.12	0.99	0.62–1.57	0.95
	Female-donor mismatch (yes vs. no)	1.21	0.80–1.85	0.37	1.37	0.91–2.07	0.13
	HLA MM A (reference: 0)						
	1 vs. 0	0.74	0.49–1.11	0.15	0.79	0.52–1.19	0.26
	2 vs. 0	0.80	0.51–1.25	0.32	0.84	0.53–1.35	0.47
	HLA MM B (reference: 0)						
	1 vs. 0	1.18	0.75–1.86	0.47	1.09	0.70–1.71	0.70
	2 vs. 0	1.14	0.71–1.83	0.58	1.00	0.62–1.62	0.99
	HLA MM DR (reference: 0)						
	1 vs. 0	1.08	0.77–1.5	0.67	1.00	0.72–1.41	0.98
	2 vs. 0	1.62	0.97–2.71	0.07	1.43	0.85–2.42	0.18
	Recipient age (1-yr increase)	1.05	1.04–1.06	<0.001	1.06	1.04–1.08	<0.001

sHR, subdistribution hazard ratio; ERSD, end-stage renal disease; ECD, expanded-criteria donors; HCV, Hepatitis C virus; PRA, panel reactive antibody; HLA MM, HLA mismatches; yr, year; Q, quartile. The bold printed covariables indicate statistical significance in the multivariable model.

considered would have a significant effect. We believe that this result emphasizes the advantage of young donors for long-term graft survival.

No clear effect of DGF on patient outcome has been reported. Some studies highlight the association between DGF and mortality, [9, 14, 17] whereas others [6, 8, 13] have not found a significant effect. None of these studies accounted for competing risks.

In our study, we confirmed this association using a standard Cox proportional hazards regression, but not when modeling cumulative incidence of the failure types (Fine and Gray models). Both approaches are valid, and the choice of the appropriate approach depends on the research question. To better understand and discuss this finding, we first give an overview of competing risks in the context of KTx.

Survival analysis involves the statistical analysis of the time to the occurrence of an event. However, in biomedical research, the need to address multiple potential outcomes is nearly ubiquitous. Competing risks are used to model a situation in which subjects under investigation are exposed to several causes of failure, such as graft failure or death with graft function. These two events are mutually exclusive, and only the first event that occurs is observed. Thus, the analysis and interpretation of competing risk data differ from survival analysis with only a single cause of failure. As such appropriate methods must be applied.

The estimated cumulative incidence of an event of interest using the 1-KM estimate is, in general, higher than estimates obtained when accounting for competing risks [19, 41, 42]. This is because when an individual experiences a competing risk event, this individual is treated as censored and is eliminated from the risk set. Censored patients are considered to have the same probability of experiencing the event as patients who remain under follow-up [41]. However, a subject who is censored due to failure from a competing risk (e.g., patient death) will clearly not experience the event of interest (allograft loss functioning). Because subjects who will never fail (by the failure of interest) are

treated as if they could fail (they are censored), the 1-km estimator overestimates the probability of failure and underestimates the corresponding survival probability [19, 42]. We confirmed this finding, especially after the 10th year of follow-up when the probability of graft failure and patient death increases.

In the competing risk context, there are different approaches to quantifying the effect of covariates in the presence of competing events [26, 43]. In the current study, the influence of DGF was evaluated using the cause-specific Cox proportional hazards regression model (modeling the cause-specific hazard) and the Fine and Gray regression model (modeling the subdistribution hazards). We found that the effect of this covariate differed between these two approaches. Both results are valid, but their interpretation is different and depends on the purpose of the study (etiology vs. prediction) [23, 42, 44, 45].

If the primary interest in the etiological question of how the covariates affect the event of interest, the cause-specific hazards model would be most appropriate, because they directly model the covariate effect on event rates among subjects at risk [28]. Using this approach in the current study, DGF significantly increases the risk of mortality (csHR = 1.57, $P = 0.029$). This hazard can be interpreted among those recipients who did not experience the event of interest (patient death), that is, those recipients who were censored because they were alive or had already been transferred for dialysis due to graft failure (competing event), but they were alive when they were censored for graft failure. Considering our example, the csHR of 1.57 means that a DGF recipient has a hazard of dying that is 1.57 higher than non-DGF recipients, when considered among recipients who were alive and who did not experience graft failure at that time.

For the purposes of prognosis and medical decision-making, the primary interest is in the absolute risks of the event of interest; therefore, the subdistribution hazards model would be more relevant [46]. This competing risk analysis allows splitting the contribution of a covariate of each event type separately. For our example, the effect of DGF did not reach conventional significance. Furthermore, the estimated effect (sHR = 1.22, $P = 0.28$) was smaller than the corresponding DGF effect obtained by standard Cox analysis (csHR = 1.57). The major advantage of the competing risks approach is that the effects of each risk factor can be estimated and formally compared across different end points.

The conflicting findings of the impact of DGF on graft and patient survival results not only from the ambiguity in the definition of DGF but also from the statistical methodology used to study its effect. The impact of DGF on two types of graft loss was assessed in this study using specific methods designed for the competing risks analysis and was compared with the results of the standard survival analysis methods. Accounting for the Fine and Gray model, DGF was not significantly associated with patient death. However, it has a significant adverse effect on the hazard of graft failure, independent of AR. The results stress the importance of using appropriate statistical methods if competing risks are present.

This article also presents an overview of competing risks concepts in the context of KTx, including the bias in the standard Kaplan–Meier estimator. Competing risks are clearly important for medical research, and their negligence has important clinical implications. The *naive* interpretation of Kaplan–Meier estimates in the presence of competing risks as estimates of actual risks leads to potential overestimation of the actuals probabilities of graft failure and patient death and overestimation and inappropriate risk stratification in prognostic models. This is markedly important in a field such as kidney transplantation, where changes in survival-influencing factors, such as immunosuppression practices, organ allocation policies, or surgical techniques, may occur rapidly and where competing events are pervasive.

Authorship

IF, LT, JM, ACH and DM: participated in the design and coordination of the study and drafted the manuscript. IF, LT, JM and DM: conducted the biostatistical analyses. LSM, LD and ACH: were involved in the data collection and management of the study. Each author contributed important intellectual content during the drafting and revision of the manuscript and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All of the authors read, revised, and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cox proportional hazard regression (cause-specific hazard model) for all possible events.

Table S2. Fine and Gray model (hazard of the subdistribution model) for all possible events.

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