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ORIGINAL ARTICLE

Impact of donor age on long-term outcomes after delayed graft function: 10-year follow-up

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Summary

Delayed graft function (DGF) has a negative impact on graft survival in donation after brain death (DBD) but not for donation after cardiac death (DCD) kidneys. However, older donor age is associated with graft loss in DCD transplants. We sought to examine the interaction between donor age and DGF in DBD kidneys. This is a single-center, retrospective review of 657 consecutive DBD recipients transplanted between 1990 and 2005. We stratified the cohort by decades of donor age and studied the association between DGF and graft failure using Cox models. The risk of graft loss associated with DGF was not significantly increased for donor age below 60 years (adjusted hazard ratio [aHR] 1.12, 1.51, and 0.90, respectively, for age <40, 41–50 and 51–60 years) but significantly increased after 60 years (aHR 2.67; $P = 0.019$). Analysis of death-censored graft failure yielded similar results for donor age below 60 years and showed a substantially increased risk with donors above 60 years (aHR 6.98, $P = 0.002$). This analysis reveals an unexpectedly high impact of older donor age on the association between DGF and renal transplant outcomes. Further research is needed to determine the best use of kidneys from donors above 60 years old, where DGF is expected.

Introduction

Delayed graft function (DGF) is known to be associated with lower graft survival in kidney transplant recipients [1–4]. In the US, its rate has increased over time from 15% in 1985–1992 to 23% in 1998–2004 and it was recently observed that receiving a kidney from a donor aged above 60 years nearly triples the risk of DGF [5,6]. Because the rate of DGF is higher in kidneys from older donors, the question has been raised whether the increased rate of DGF because of wider use of extended criteria donors (ECD) will translate into poorer long-term outcomes [5]. With the goal to improve organ allocation and outcomes, risk prediction nomograms have been developed to identify both donor and recipients factors associated with DGF [6,7].

In parallel, accumulating data on kidneys procured following donation after cardiac death (DCD) show that there is no impact of DGF on graft survival in this group, despite a risk of DGF being twofold greater than for donor after brain death (DBD) recipients [8,9]. Interestingly however, it was demonstrated that among the criteria used to define ECD, donor age is the only independent predictor of graft loss in DCD kidneys [10]. Whether increasing donor age differentially affect the association between DGF and survival has not been explicitly examined to date.

In light of these observations, we tested the hypothesis that in DBD recipients, donor age modifies the impact of DGF on long-term outcomes. Specifically, we hypothesized that DGF in recipients of kidneys from older donors would be associated with poorer graft survival as compared with DGF occurring in kidneys from younger donors.

Patients and methods

Study design and population

This is a single-center, retrospective cohort study. All subjects who received a kidney transplant from a deceased donor in our center between January 1, 1990 and July 1, 2005 were eligible. During this period, there were no DCD kidneys procured. Exclusion criteria were [1] patients younger than 18 years and [2] primary nonfunction because of technical failure, defined as an absence of renal function following transplant secondary to a surgical complication at the time of transplant. Follow-up period was continued until September 1, 2011. Routine clinical follow-up was conducted in our center for all patients. Clinical data were prospectively collected on a biannual basis and graft survival on a weekly basis in an electronic database, either by the transplant nephrologist or a research nurse. No patients were lost to follow-up.

Interleukin-2 receptor inhibitor was used for induction therapy according to the attending transplant nephrologist. No other induction was used in any patient. All grafts were statically preserved in cold University of Wisconsin solution, without pulsatile preservation. All patients gave their prior consent to the study at the time of enrolment on the waiting list in accordance with Quebec Transplant institutional review board.

Definitions of exposure and outcomes

Delayed graft function was defined as the need for dialysis in the first 7 days following transplant. The two outcomes studied were [1] total graft failure, defined as either death regardless of graft function or a return to dialysis and [2] death-censored graft failure, defined as a return to dialysis.

Statistical analyses

Clinical characteristics between subjects with and without DGF were compared using unpaired *t*-test or Fisher's exact test for continuous and categorical data respectively. Causes of graft loss were compared using chi-squared test. To examine for potential effect modification of age on the relation between DGF and graft survival, we first stratified the cohort by decades of donor age into four categories: below 40 years, 41–50 years, 51–60 years, and above 60 years. The reason to explore decades of age as cohort boundaries was based on previous observations made by Locke *et al.*, showing that DCD kidneys from donors older than 50 years have an adjusted hazard ratio of 1.8 for graft loss compared to DCD kidneys from donors younger than 50 years [10]. Within each stratum, the relation between DGF and graft survival was first assessed using Kaplan–Meier method and log-rank test. Unadjusted and adjusted Cox proportional hazards models were used to model the risk of graft failure in relation to DGF, with the use of interaction terms for donor age and DGF. Multivariable models were adjusted for the potential confounders identified in the analysis of the baseline characteristics between subjects with and without DGF (Table 1): recipient age, recipient diabetes status at the time of transplant, recipi-

Table 1. Clinical characteristics of the study population

	DGF (n = 122)	No DGF (n = 535)	P-value
Recipient			
Age (years)	46 ± 13	44 ± 13	0.077
Male gender	85 (70)	358 (67)	0.668
HLA A-B-DR mismatch	2.9 ± 1.0	2.7 ± 1.1	0.144
PRA (%)	8 ± 17	6 ± 15	0.256
First transplant	110 (90)	479 (90)	1.000
Time on dialysis (mo)	37 ± 45	26 ± 32	0.002
Diabetes	26 (21)	71 (13)	0.033
BMI (kg/m^2)*	26.3 ± 5.1	24.7 ± 4.2	<0.001
Warm ischemia time (min)	37 ± 11	34 ± 8	0.002
Cold ischemia time (h)	25 ± 8	20 ± 6	<0.001
Induction	36 (30)	73 (14)	<0.001
Maintenance immunosuppression			
Corticosteroids	122 (100)	535 (100)	1.000
Calcineurin inhibitor	120 (98)	520 (97)	0.751
MMF or azathioprine	71 (58)	309 (58)	0.920
Sirolimus	0 (0)	8 (2)	0.363
Donor			
Age (years)	43 ± 20	37 ± 18	0.002
Age			
Below or equal to 40	49 (40)	284 (53)	<0.001
41–50	22 (18)	122 (23)	
51–60	20 (16)	70 (13)	
Above 60	31 (25)	59 (11)	
Male gender	70 (57)	300 (56)	0.840
Serum creatinine – μmol/l	84 ± 33	76 ± 27	0.003
eGFR (ml/min/1.73 m^2)†	90 ± 33	104 ± 37	<0.001

DGF, delayed graft function; PRA, panel-reactive antibody; BMI, body-mass index; MMF, mycophenolate mofetil; eGFR, estimated glomerular filtration rate.

Data are provided as mean ± standard deviation or n (%). Comparisons were performed using unpaired t-test or Fisher's exact test.

*BMI was available only for 87 subjects with DGF and 429 subjects without DGF.

†Estimated using the modification of diet in renal disease (MDRD) equation.

ent weight, time on dialysis, cold ischemia time, warm ischemia time, induction therapy, and donor-estimated glomerular filtration rate (eGFR) measured by the Modification of Diet in Renal Disease (MDRD) equation. Violations of the proportional hazards assumption were examined by plots of the logarithm of the negative logarithm of the estimated survivor function versus log time. Longitudinal comparisons of eGFR over time were conducted using generalized estimating equations and the results were adjusted for the above mentioned covariates. For this analysis, an eGFR value of zero was imputed for subjects with a failed graft for each time point following graft loss. Statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX, USA). All tests were two tailed, and a $P < 0.05$ was considered statistically significant.

Table 2. Causes of death and graft loss.

	Total	With DGF	Without DGF	*P*-value
Deaths	110	23	87	0.388
Cardiovascular	38 (35)	10 (44)	28 (32)	
Neoplasic	27 (25)	3 (13)	24 (28)	
Infectious	10 (9)	1 (4)	9 (10)	
Mixed	7 (6)	1 (4)	6 (7)	
Others	28 (26)	8 (35)	20 (23)	
Graft losses	85	28	57	0.293
Rejection	48 (57)	15 (54)	33 (58)	
Infectious	7 (8)	3 (11)	4 (7)	
Mixed	17 (20)	8 (29)	9 (16)	
Others	13 (15)	2 (7)	11 (19)	

DGF, delayed graft function.
Data are provided as *n* (%). Comparisons were performed using chi-squared test.

Results

Baseline clinical characteristics

A total of 657 participants received a single or dual kidney transplant from a DBD between January 1990 and July 2005 and met the study criteria. Among these, 122 (19%) subjects experienced DGF post-transplant. Table 1 shows the baseline donor and recipient characteristics by DGF status. Compared with subjects who did not need postoperative dialysis, those with DGF spent more time on dialysis pretransplant, were more likely to be diabetic, and more received induction therapy at the time of transplant. Mean warm and cold ischemia times were significantly longer in subjects with DGF. Donors of recipients with DGF were older and had a lower eGFR at the time of organ procurement.

Total graft survival by donor age and DGF status

Median length of follow-up was 106 months (minimum and maximum, 1–233 months). As displayed in Table 2, 195 graft losses (29.7%), including 110 (16.7%) deaths with a functioning graft, were recorded during this period. There was no difference in the cause of death between the groups. To verify if donor age modifies the effect of DGF on graft outcomes, we first stratified the cohort by decades of age, beginning at 40 years and stratifying up to 60 years. As shown in Fig. 1 and Table 3, the unadjusted analysis showed a moderate increase in graft loss in association with DGF within the three strata less than 60 years of age and a clear association between the two variables when donor age was above 60 years.

Table 3 shows the association between DGF and total graft failure after adjustment for recipient age, recipient diabetes status, recipient weight, time on dialysis, induction therapy, donor eGFR, and cold and warm ischemia times. The Cox proportional hazards model revealed that the risk of graft loss was more than 2.5-fold higher among recipients of a kidney that experienced DGF in the case of donors above 60 years old ($P = 0.019$). Based on these observations, we examined the effect modification of donor age above 60 years on the relationship between DGF and uncensored graft loss in the adjusted model and found a trend towards a significant interaction (interaction $P = 0.095$).

Death-censored graft survival by donor age and DGF status

Among the graft losses seen in this population, 48 (57%) were because of rejection, 7 (8%) to infection, and 17 (20%) to a combination of both (Table 2). There was no difference between subjects with and without DGF with regards to the causes of graft loss. As shown in Fig. 2 and Table 4, the unadjusted analysis of death-censored graft survival stratified by donor age again revealed a striking difference in the effect of DGF on graft outcomes between recipients of a kidney from a donor younger versus older than 60 years. Adjusted models showed that, whereas hazard ratios for graft loss varied from 1.21 to 1.93 within the strata of donors under 60 years, the hazard ratio was 6.98 (95 percent confidence interval, 2.02–24.11) for donors above that age. The p-value for interaction between donor age above 60 years and DGF in the uncensored graft failure analysis was statistically significant ($P = .019$).

Additional analyses were performed to evaluate the robustness of the findings. First, we built a model including the following additional covariates: recipient gender, peak panel-reactive antibody level, first versus repeat transplant, and cause of death. Second, because the cohort was assem-

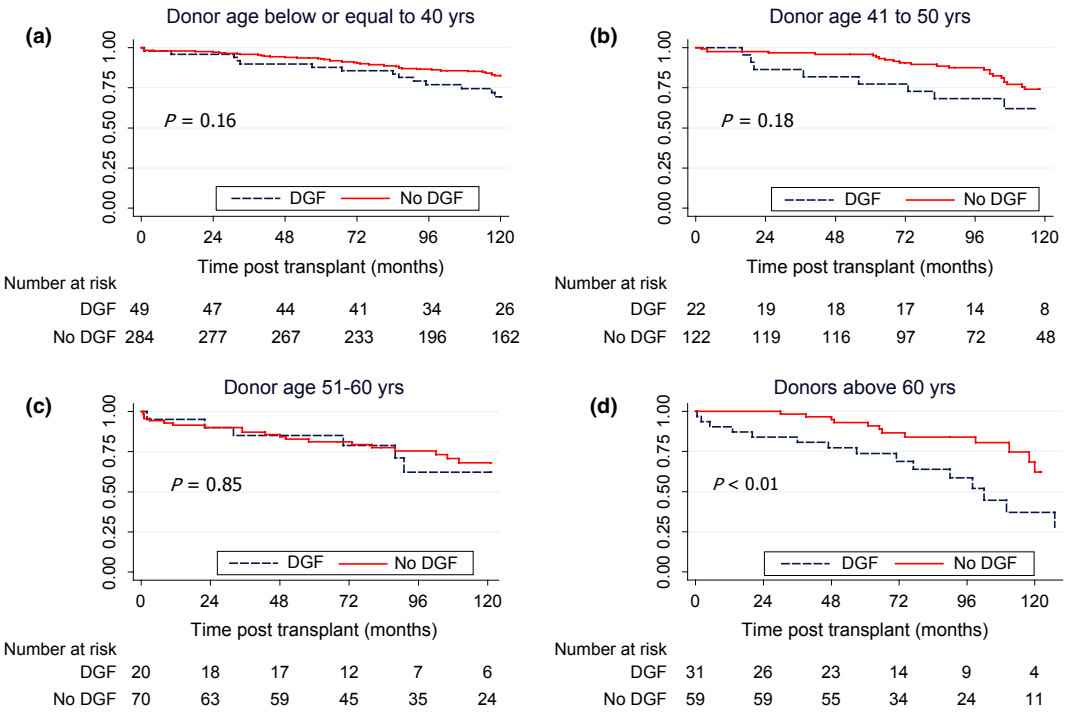

Figure 1 Kaplan–Meier plots of graft survival by DGF status. The cohort is stratified by donor age so that graft survival is shown for recipients of kidneys from donors aged (a) ≤ 40 years, (b) 41–50 years, (c) 51–60 years, and (d) >60 years. Comparisons were performed using log-rank test.

bled over a long period of time, we added a covariate adjusting for immunosuppression era, defined by the time of introduction of mycophenolate mofetil as maintenance therapy. In both cases, results were similar to those obtained in the original analyses. Third, we stratified the cohort according to ECD status instead of donor age. Adjusted hazard ratios (95 percent confidence interval) for total graft failure were 1.16 (0.76–1.78) and 1.76 (0.87–3.57) for non-ECD and ECD recipients, respectively, and 1.57 (0.83–2.97) versus 3.30 (1.27–8.59), respectively, for death-censored graft failure.

Longitudinal graft function

Figure 3 displays eGFR up to 10 years post-transplant according to DGF status. Subjects were stratified according to donor age below or equal to 60 years versus above 60 years. In recipients of kidneys from donors above 60 years, DGF was associated with a lower initial eGFR at hospital discharge and a greater decline over time (19 ± 21 vs. 25 ± 20 ml/min; interaction $P = 0.038$). In contrast, in recipients of kidneys from donors 60 years old or younger, there was a lower initial eGFR, but a similar decline in graft

Table 3. Univariate and multivariate risk estimates for total graft failure associated with DGF.

			Unadjusted model		Adjusted model†	
Donor age	Subjects	Events	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All subjects	657	195	1.67 (1.21–2.29)	0.002	1.37 (0.96–1.95)	0.085
Stratification by donor age*						
<40 years	333	96	1.42 (0.87–2.33)	0.163	1.12 (0.64–1.95)	0.692
41–50 years	144	42	1.63 (0.80–3.33)	0.181	1.51 (0.65–3.53)	0.338
51–60 years	90	27	1.09 (0.44–2.73)	0.848	0.90 (0.33–2.40)	0.826
>60 years	90	30	2.82 (1.34–5.96)	0.006	2.67 (1.17–6.09)	0.019

DGF, delayed graft function; HR, hazard ratio.

*Within each strata, hazard ratio is for DGF vs. no DGF.

†Adjusted for: recipient age, recipient diabetes status at the time of transplant, recipient weight, time on dialysis, induction therapy, donor eGFR, cold ischemia time, warm ischemia time. Analysis was performed using Cox proportional hazards models.

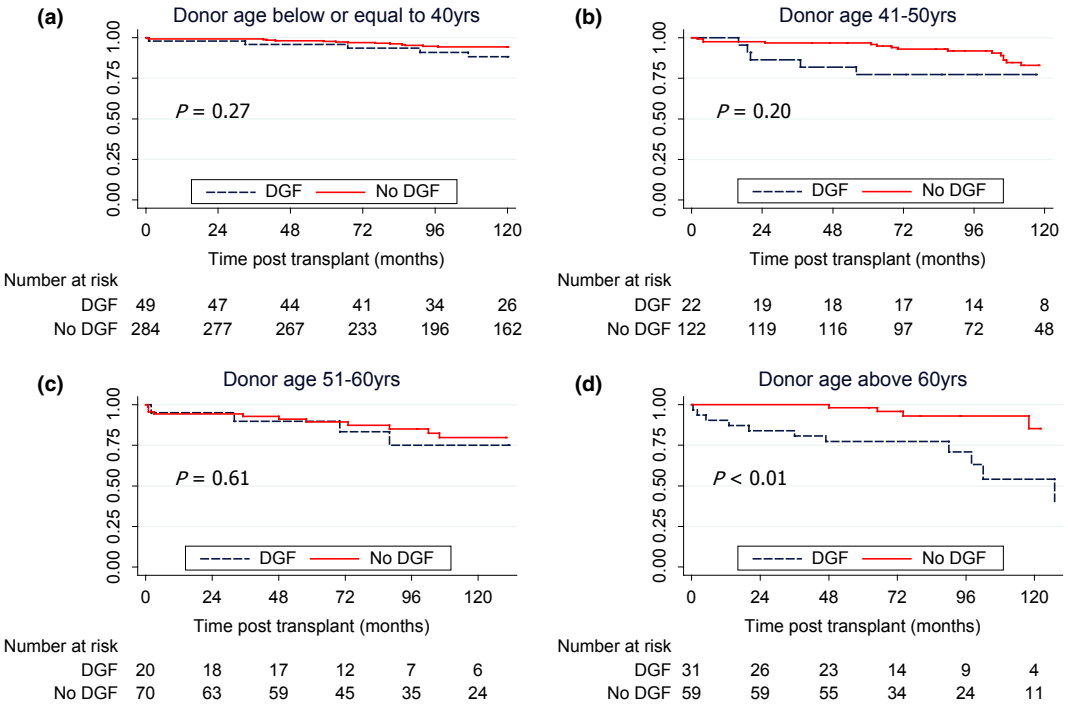

Figure 2 Kaplan–Meier plots of death-censored graft survival by DGF status. The cohort is stratified by donor age so that graft survival is shown for recipients of kidneys from donors aged (a) ≤40 years, (b) 41–50 years, (c) 51–60 years, and (d) > 60 years. Comparisons were performed using log-rank test.

Table 4. Univariate and multivariate risk estimates for death-censored graft failure associated with DGF.

			Unadjusted model		Adjusted model†	
Donor age	Subjects	Events	HR (95% CI)	*P*-value	Donor age	Subjects
All subjects	657	85	2.33 (1.48–3.66)	<0.001	2.12 (1.28–3.52)	0.004
Stratification by donor age*						
<40 years	333	31	1.60 (0.69–3.71)	0.277	1.50 (0.59–3.85)	0.395
41–50 years	144	24	1.81 (0.72–4.58)	0.209	1.93 (0.64–5.84)	0.244
51–60 years	90	15	1.35 (0.43–4.23)	0.613	1.21 (0.34–4.33)	0.768
>60 years	90	15	6.39 (2.03–20.12)	0.002	6.98 (2.02–24.11)	0.002

DGF, delayed graft function; HR, hazard ratio.
*Within each strata, hazard ratio is for DGF versus no DGF.
†Adjusted for: recipient age, recipient diabetes status at the time of transplant, recipient weight, time on dialysis, induction therapy, donor eGFR, cold ischemia time, warm ischemia time. Analysis was performed using Cox proportional hazards models.

function at 10 years post-transplant (10 ± 14 vs. 11 ± 14 ml/min; interaction $P = 0.803$).

Discussion

Kidney transplantation is now firmly established as the standard of care for patients of all ages developing end-stage renal disease [11,12]. To meet the growing demand of organs, kidneys from expanded criteria donors have been increasingly used. Although these organs provide better survival than remaining on dialysis, their outcomes are inferior to kidneys from standard criteria donors [13,14]. Identifying modifiable factors to improve the selection and outcomes of these organs would be of clear benefit. Here, we demonstrate that the effect of DGF on long-term graft survival is modified by donor age. We found that the negative impact of DGF on long-term graft survival was worse for recipients of kidneys from donors aged above 60 years as compared with recipients from younger donors. This association persisted after adjustment for baseline clinical

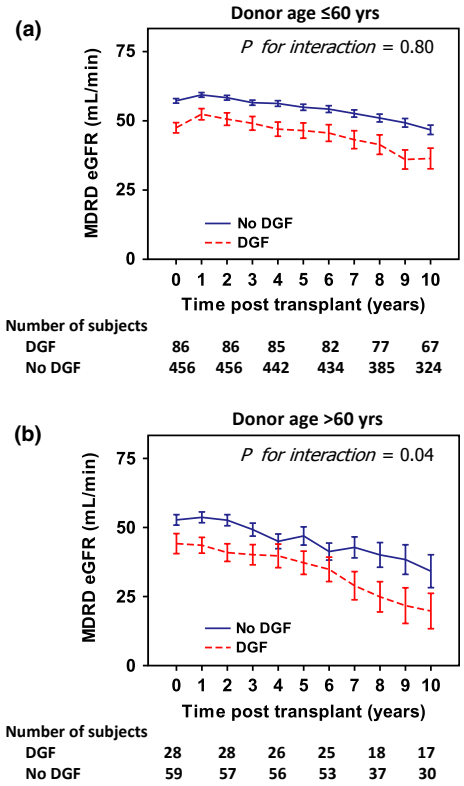

Figure 3 Longitudinal graft function over time by DGF status. Mean eGFR ± SEM is shown for each time point for recipients of a kidney from a donor aged (a) ≤60 years or (b) >60 years. There was a statistically significant effect of time between subjects with and without DGF when donor age was above 60 years. *P*-values were calculated using generalized estimating equations.

characteristics that differed between recipients who experienced DGF and those who did not.

The overall incidence of DGF in our population was 19%, which is comparable to recent data from UNOS [5], and the hazard ratio of 1.37 for graft loss in the whole cohort of patients is similar to the results of a recent meta-analysis, in which the risk ratio associated with DGF was 1.41 at 3 years post-transplant [15]. The negative impact of DGF on kidneys procured from old donors might not be surprising if one considers the poorer outcome of acute kidney injury (AKI) in the elderly. DGF is an ischemic injury likely to be reversible in kidneys with normal function. However, several large studies demonstrated that, compared with younger patients, elderly patients are at increased risk of end-stage renal disease following AKI. It has also been suggested that age should be recognized as a potential effect modifier in the prognosis after AKI [16–18].

The magnitude of the effect modification of DGF by donor age was more important for the risk of death-censored graft failure compared with total graft failure. This finding is not surprising, since DGF is a major nonimmunologic factor in the development of chronic allograft dysfunction, which is strongly related to the lifespan of the graft [19,20]. Nonetheless, it was recently observed in a population of kidney transplant recipients receiving rabbit antithymocyte globulin induction that, although DGF was associated with lower graft survival at 3 years post-transplant, death-censored graft survival was not related to DGF [3].

Our findings may have important clinical implications for centers using marginal kidneys. Although the use of kidneys from expanded criteria donors has been shown to be safe, one of the key questions about these organs is how to improve their selection and preservation to maximize their outcome. There is a need to elucidate factors that can be identified pretransplant to either guide organ preservation or to help judiciously discard kidneys from older donors at an unacceptably increased risk of graft failure. Our results suggest that, above and beyond the traditional risk factors identified in large database studies and recently included in a predictive nomogram available online [7], there might be additional factors that could be identified.

It might be hypothesized that the effect of factors related to tissue hypoxemia before organ procurement could be captured by the change in the donor's serum creatinine pretransplant. However, it is clear that, within the short period of time spent by the donors in the intensive care unit (ICU), serum creatinine may not have time to increase even though severe acute kidney injury occurred. It is thus conceivable that factors such as the duration of cardiopulmonary resuscitation, the use of vasopressors or the length of stay in the ICU [21], could be used as prognostic factors for kidneys from older donors. One caveat common to such variables is that reliable quantification might be difficult to obtain in a useful manner. Among other potential tools available to predict the risk of DGF, assessment of the organ quality by measuring perfusion flow and resistive indices on machine perfusion is increasingly used, but it was recently shown to have a low predictive value in a prospective study including over 300 kidneys [22,23]. However, prospective studies show that pulsatile perfusion preservation could especially be useful for ECD kidneys, as it can reduce by more than threefold the incidence of DGF in these organs and improve their outcomes [24–26]. Microarray studies of the transcriptome of the graft have been suggested as a way to identify kidneys at increased risk of DGF [27]. One obvious limitation to such techniques is the feasibility of getting the analysis done in a timely manner to guide kidney allocation.

Our study has some limitations. First, DGF was defined by the need for dialysis in the first 7 days post-transplant. This definition does not only capture slower graft function, but also hyperkalemia or volume overload, which might occur despite a relatively good kidney function post-transplant. However, it has been the one most commonly used

in the literature and offers the advantage of being objective and reproducible [5]. Second, the results presented are based on a limited sample size. However, the magnitude of the observed association makes it unlikely that residual confounding would completely explain our findings. Third, the data acquisition extends over a long period of time, during which criteria for organ allocation have changed, most notably for marginal kidneys. However, the increase in the use of ECD in the recent years means that most of the kidneys from donors above 60 years old have been transplanted in the current era of immunosuppression and clinical management. Hence a bias because of temporal change in kidney selection would probably favor better outcomes for ECD kidneys and thus is unlikely to explain our results. Nonetheless, bias secondary to organ allocation in relationship to donor and recipient characteristics might be influenced by local practices and thus is difficult to ascertain. Finally, insufficient data were available to conduct an analysis of outcomes for donors aged above 70 years. This is a population worth examining separately, since recent data suggests a higher risk of graft loss and patient death in this group compared with donors aged 50–69 years [28].

In summary, although DGF is a known risk factor for graft loss in kidney transplant recipients, its effect seems to be modulated by donor age, with a substantially higher negative impact in donors above 60 years old. Further studies are needed to better assess the factors associated with the occurrence of DGF in this population, to determine if they could be used to guide kidney allocation and reduce the risk of graft failure.

Authorship

IL: participated in study design, data analysis, and article writing. JGL: participated in study design, data analysis, and article writing. RN participated in interpretation of data. IC: participated in study design and data analysis. YC: participated in interpretation of the data. MA: participated in data analysis and article writing. IH: participated in study design, data analysis, and article writing. MRG: participated in data collection and interpretation of data. SJK: participated in data analysis and article writing. SADS: participated in design of the study and overlooked data analysis and article writing.

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