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A useful scoring system for the prediction and management of delayed graft function following kidney transplantation from cadaveric donors

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Delayed graft function (DGF) is a common complication in kidney transplantation and is known to be correlated with short- and long-term graft outcomes. Here we explored the possibility of developing a simple tool that could predict with good confidence the occurrence of DGF and could be helpful in current clinical practice. We built a score, tentatively called DGFS, from a French multicenter and prospective cohort of 1844 adult recipients of deceased donor kidneys collected since 2007, and computerized in the Données Informatisées et VAlidées en Transplantation databank. Only five explicative variables (cold ischemia time, donor age, donor serum creatinine, recipient body mass index, and induction therapy) contributed significantly to the DGF prediction. These were associated with a good predictive capacity (area under the ROC curve at 0.73). The DGFS calculation is facilitated by an application available on smartphones, tablets, or computers at www.divat.fr/en/online-calculators/dgfs. The DGFS should allow the simple classification of patients according to their DGF risk at the time of transplantation, and thus allow tailored-specific management or therapeutic strategies.

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Within the past decade, while the frequency of acute allograft rejection episodes has dramatically decreased under modern immunosuppressive regimens,[1] the incidence and severity of delayed graft function (DGF) has remained stable. The DGF is generally defined by the need for dialysis within the first seven days post transplantation,[2] its frequency range from 25 to 50%[3] possibility explained by the lack of a single definition and/or the more widespread use of expanded criteria donors (ECDs) or non-heart-beating donors.[3] DGF is known to be associated with a lower one-year post transplantation renal function, a decreasing long-term graft and recipient survival, and an increasing patient management cost.[4,5]

Reducing the incidence of DGF by controlling risk factors related to both donors and recipients is among the most beneficial strategies.[6,7] Providing drugs is also promising either in pre-clinical studies[8–11] or using already well-known immunosuppressive therapy such anti-thymocyte globulin (ATG).[12–14] Nevertheless, these therapeutic strategies are still under debate.[15–18] To propose strategies to prevent the occurrence of a DGF for a better management of kidney transplantation recipients, it is of importance to screen as far as possible patients at-risk of DGF.

Several DGF-scoring systems have been proposed within the last few years. First published in 2003[19] and then refined in 2010,[20] from the United State Renal Data System registry, Irish *et al.* proposed a predictive score that could be calculated using 18 parameters at the time of transplantation (human leukocyte antigen (HLA) mismatch, donor serum creatinine, donor age, donor weight, peak panel reactive antibodies (PRAs), recipient previous transplant, cold ischemia time (CIT), warm ischemia time, recipient race, pre-transplant

dialysis, single organ transplant, donor cause of death, non-heart-beating donor, donor hypertension, recipient gender, diabetic recipient, pre-transplant transfusion, and recipient body mass index (BMI)), with an area under the receiver-operating characteristic curve (AUC) at 0.70. Despite the high quality of this methodology, this predictive model was developed and validated from North American recipients, whereby the patients' profile differs substantially from European recipients. For instance, according to the OPTN & SRTR annual report of 2011, 30% of kidney transplantations were from living donors, 25% of the deceased donors were older than 50 years, 62% of US recipients received a depleting induction therapy, and 17% received no induction therapy compared with 13%, 58%, 53%, and 8%, respectively in the DIVAT (Données Informatisées et VAlidées en Transplantation) cohort that gathers 30% of the French kidney recipients throughout France.

No decision threshold is proposed to use the Irish score to classify patients according to their DGF risk. Jeldres *et al.*[21] proposed a simpler but equally accurate scoring system (six variables, AUC = 0.74); however, these results were based on a monocentric study of North American recipients transplanted since 1979. Finally, both scoring systems,[20,21] did not take into account the induction therapy.

We thus proposed to develop a complementary DGF score (DGFS), from DIVAT with patients transplanted since 2007. The DGFS allows to predict, with a good confidence, which patients will be at high risk of DGF according to only five variables at the transplantation time and possibly use it as a decision-making tool to decide which induction therapy could be prescribed according to the individual DGF risk profile.

RESULTS

Donor, recipient, and renal transplant characteristics

Qualitative and quantitative variables are described according to the training and validation samples in Tables 1 and 2. As the allocation was random, the two groups were similar. In the training sample used for the scoring system definition, the mean age of recipients was 51.9 (± 13.2) years and 60.4% were men. For 30.2% of the recipients, the primary indication for renal transplantation was a possible recurrent disease of the renal graft. For 20.6% and 4.5% of them, it was respectively a second transplantation and a third or more transplantation. The mean duration in dialysis before transplantation was 4.1 (± 3.9) years. Historical anti-HLA class I and II PRAs were detectable in 37.8% and 36.0% of the patients, respectively. Equal to or more than five HLA incompatibilities on A-B-DR loci were observed in 10.7% of the recipients. The mean donor age was 51.9 (± 15.6) years, 58.6% were men and 57.9% were dead because of a vascular cause. The mean terminal serum creatinine was 91.0 (± 60.7) µmol/l. The mean duration of CIT was 19.2 (± 7.0) h. A total of 25.4% of the recipients had a DGF.

Construction of the DGF predictive score

In the univariate analyses detailed in the web (Supplementary Table S1 online), possible risk factors of DGF ($P < 0.20$) were identified: donor serum creatinine, recipient age, duration of dialysis before transplantation, donor gender, number of previous transplants, immunosuppressive induction therapy, history of cardiovascular events (except HTA) and dyslipidemia, donor treatment with epinephrine and duration of CIT, donor age, and recipient BMI. Without taking into account the other risk factors, the CIT was the main predictor of DGF. More precisely, the odds ratio (OR) was multiplied by 1.05 for each hour (95% confidence interval (CI) = (1.04, 1.07)). The corresponding AUC was 0.60 (95% CI = (0.56, 0.64)).

The results of the final model are presented in Table 3. Five independent explicative variables seemed significantly associated with the risk of DGF. As expected, the probability of DGF increased with the CIT (OR = 1.06, $P < 0.0001$). High recipient BMI was also associated with higher DGF probability ($P = 0.0004$). An increase in donor age of 10 years was associated with an OR multiplied by 1.16 ($P = 0.0014$). Higher risk of DGF was observed when induction therapy was not ATG-based (OR = 1.70, $P = 0.0001$), and if donor creatinine levels were higher than 108 µmol/l (OR = 1.76, $P = 0.0004$). The induction with ATG can be analyzed according to two different protocols depending on inter-center variability: delayed ($n = 289$) or non-delayed ($n = 160$) introduction of calcineurin inhibitors. We did not distinguish between these treatment protocols in the score as the corresponding risks of DGF were not significantly different ($P = 0.7704$).

The corresponding DGFS can be calculated as follows: (1) by multiplying the logarithm of the OR and the values of the

Table 1 | Recipient, donor, and kidney transplant continuous characteristics (minimum, maximum, mean, and standard deviation) at time of transplantation according to both training and validation samples

	Training ($n = 1238$)				Validation ($n = 606$)			
	Minimum	Maximum	Mean	s.d.	Minimum	Maximum	Mean	s.d.
Cold ischemia time (hours)	6.00	58.62	19.21	7.02	6.33	47.30	18.99	6.80
Recipient age (years)	19.00	84.00	51.92	13.19	19.00	84.00	51.96	12.77
Donor age (years)	4.00	88.00	51.91	15.60	1.00	90.00	52.92	40.72
Body mass index (kg/m^2)	14.20	46.57	24.07	4.44	14.87	38.58	24.23	4.16
Donor serum creatinine (µmol/l)	20.00	999.00	91.02	60.67	20.00	335.00	86.39	44.93
Duration in dialysis (years)	0.02	36.60	4.07	3.92	0.04	34.02	3.79	3.64