Predictive Score Model for Delayed Graft Function Based on Easily Available Variables before Kidney Donation after Cardiac Death

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Abstract

Background: How to evaluate the quality of donation after cardiac death (DCD) kidneys has become a critical problem in kidney transplantation in China. Hence, the aim of this study was to develop a simple donor risk score model to evaluate the quality of DCD kidneys before DCD.

Methods: A total of 543 qualified kidneys were randomized in a 2:1 manner to create the development and validation cohorts. The donor variables in the development cohort were considered as candidate univariate predictors of delayed graft function (DGF). Multivariate logistic regression was then used to identify independent predictors of DGF with $P < 0.05$. Date from validation cohort were used to validate the donor scoring model.

Results: Based on the odds ratios, eight identified variables were assigned a weighted integer; the sum of the integer was the total risk score for each kidney. The donor risk score, ranging from 0 to 28, demonstrated good discriminative power with a C-statistic of 0.790. Similar results were obtained from validation cohort with C-statistic of 0.783. Based on the obtained frequencies of DGF in relation to different risk scores, we formed four risk categories of increasing severity (scores 0–4, 5–9, 10–14, and 15–28).

Conclusions: The scoring model might be a good noninvasive tool for assessing the quality of DCD kidneys before donation and potentially useful for physicians to make optimal decisions about donor organ offers.

Key words: Delayed Graft Function; Donation after Cardiac Death; Kidney Transplantation; Predictive Score

INTRODUCTION

Donation after cardiac death (DCD) is becoming the main source of organ transplantation in China.^[1,2] One of the major concerns regarding the increasing use of kidneys from DCD donors is the high incidence of delayed graft function (DGF) and high risk of early graft dysfunction and failure observed in such transplants.[3‑5] Physicians consider DGF to be a clinical challenge because it predisposes the kidney to rejection and decreases graft survival.^[6] Therefore, how to assess the quality of DCD kidneys before transplant and decide whether or not to abandon the kidney is a critical problem for kidney transplant surgeons.

Kidney biopsy has been used as a gold standard for assessing kidney quality before transplantation until now. However, kidney biopsy is a time‑consuming and invasive

process that requires experienced pathologists to assess kidney quality. Therefore, there is an urgent need for a noninvasive and easy way to assess the quality of DCD kidneys, which might help physicians initiate preventive therapeutic strategies in recipients who receive organs at

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an increased risk for DGF. In this regard, several predictive models for DGF have been developed within the last few years.[5,7‑11] These models contribute to the prediction and evaluation of kidney function in China DCD, however, not entirely suitable for China DCD. Therefore, it is of great significance to identify DGF by simple and easily accessible pretransplant variables.

In this study, the aim was to develop a simple donor risk score model that could be readily applied by physicians to evaluate the quality of DCD kidneys and identifies kidneys at the highest risk of DGF before DCD.

Methods

Ethical approval

The local institutional review board of the First Affiliated Hospital of Xi'an Jiaotong University approved the study protocol, which was in compliance with the provisions of the current *Declaration of Helsinki* principles and good clinical practice guidelines. All patients provided written informed consent for participation in the study and to have their medical data used for research purposes.

Study populations

We retrospectively reviewed the effects of all consecutive patients aged between 16 and 70 years who underwent primary DCD kidney transplantation at the First Affiliated Hospital of Xi'an Jiaotong University between December 1, 2011, and October 31, 2016. Recipients were excluded from the study if: (1) they had undergone re-transplantation, received an organ other than a kidney, or developed graft failure within 48 h of the transplant operation; (2) had a positive cross match or positive panel‑reactive antibody (over 30%); (3) had an active infection, hepatitis, or abnormal hepatic function; or (4) had leukopenia (leukocytes <3000/mm³), thrombocytopenia (platelets <100,000/mm3), or severe anemia (hemoglobin <60 g/L). DCD donor inclusion criteria are the following: (1) identity, (2) negative HIV antigen test, (3) $16 \le$ age ≤ 65 years, and (4) negative diagnosis for the malignant tumor, drug abuse, or renal diseases.

Clinical data collection

Qualified patients from the entire database were randomized in a 2:1 manner to create development and validation cohorts, respectively. Patient and donor data were collected in electronic clinical patient charts. Based on previous studies[8,10,12] and our experience, the following risk factors were collected: donor characteristics (age, sex, cause of death [COD], history of hypertension of diabetes, before donation estimated glomerular filtration rate [eGFR], hypotension process, vasopressor used, and cardiopulmonary resuscitation [CPR] event), cold and warm ischemia time, and recipient characteristics at the time of transplantation (age, sex, number of previous kidney transplantations, preexisting kidney disease, and number of human lymphocytic antigen mismatches). Graft outcome data were also recorded. DGF was defined as the need for dialysis within the 1st week after transplantation. Graft failure was

defined as return to hemodialysis, transplant nephrectomy, or recipient death with a functioning graft.

Immunosuppressant protocol

A triple immunosuppressive regimen was used in all patients of mycophenolic acid, calcineurin inhibitor, and prednisone. All patients received either basiliximab or rabbit antithymocyte globulin (ATG) as an induction therapy. Basiliximab was given at a dose of 20 mg on postoperative days 0 and 4. ATG was given at 1.25 mg·kg⁻¹ d⁻¹ starting during the operation and for 3–5 days postoperatively.

Statistical analysis

Qualitative variables were presented as frequencies and percentages, and quantitative variables were presented as the means \pm standard deviation (SD) or median. The donor risk score development cohort was initially used for identifying univariate associations between donor variables and DGF. Multivariate logistic regression analysis was then performed to identify independent predictors of DGF and to estimate odds ratios(*OR*s). The estimated *OR*s from the logistic model were used, giving an integer of 1 to each 0.5 value of *OR*. Donor variables that were significant in the univariate analysis were available for selection in the final model; a total of 1000 bootstrap samples were selected from the development cohort for the best subset of risk factors to avoid overfitting the data. For each sample, a stepwise selection procedure was used to choose independent predictors of DGF. Variables that were selected in ≥90% of the bootstrap models were included in the final multivariate models, the scoring method similar to that of Sullivan *et al*. [13] The predictive accuracy of the risk score was assessed by both discrimination measured by receiver operating characteristics curves and compared their C‑statistics (area under the curve) and calibration evaluated by Hosmer–Lemeshow Chi-squared statistic.^[14] The results were considered statistically significant for $P \le 0.05$. All calculations were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of donors and recipients

During the study period, 543 recipients of kidney transplant from DCD were recorded. Qualitative and quantitative variables were described according to the development ($n = 362$) and validation $(n = 181)$ cohorts as summarized in Table 1. As the allocation was random, the two groups were similar. The most common COD about donors in both groups was craniocerebral trauma (62.3% vs. 61.9%, respectively, $P = 0.932$), and the eGFR in donors immediately before organ procurement was slightly lower in development cohort versus validation cohort $(92.8 \pm 60.1 \text{ vs. } 96.5 \pm 65.9 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, respectively, $P = 0.537$. There were no significant differences about demographic and clinical characteristics between these two groups with respect to donors and recipients [Table 1]. The immunosuppressive regimen and induction program in two groups had no significant difference.

Data are presented as mean \pm SD or *n* (%). *PRA <10% was negative; 10%) PRA <30% was considered positive; PRA ≥30% was excluded from this study, † In the two groups, 172 donors were identical. BMI: Body mass index; PRA: Panel-reactive antibody; CPR: Cardiopulmonary resuscitation; eGFR: Estimated glomerular filtration rate; SD: Standard deviation; DCD: Donation after cardiac death; HLA: Human lymphocytic antigen; HMP: Hypothermic machine perfusion.

Uni‑ and multi‑variate analyses of donor variables associated with delayed graft function in development cohort

Since this study focused on the donor risk factors before kidney donation, some of the receptors and postdonation risk factors are not included in the analysis. Based on previous studies, we selected 12 commonly used donor risk factors for DGF to analysis[Table 2]. Eight donor variables (COD, history of hypertension, terminal eGFR, age, history of diabetes, hypotension process, vasopressor used, and CPR event) were found by univariate analysis to be significantly associated with DGF [Table 3]. All

*Blood pressure ≤80 mmHg before donation during hospitalization; † CPR occurred during hospitalization and before donation and successful recovery. CPR: Cardiopulmonary resuscitation; DGF: Delayed graft function; ICU: Intensive Care Unit; BMI: Body mass index.

the others (donor sex, right or left kidney, Intensive Care Unit [ICU] stay time, and body mass index [BMI]) were excluded at $P > 0.10$. To better identify the predictors of DGF, we built a multivariate logistic regression model including all the variables significantly associated with DGF at univariate analyses. Seven factors (age, history of hypertension, hypotension process, COD, terminal eGFR, vasopressor used, and CPR event) were significantly associated with DGF on multivariate analysis [Table 3]. The history of diabetes approached significance in the multivariate analysis $(P = 0.058)$.

Construction of the delayed graft function predictive score model

The methods of Sullivan *et al*. [13] were used to convert the model in Table 4 to a simple point system. The risk score was derived from a competing risk model with DGF in Table 3. To calculate the risk score, points for all factors are summed. According to the results of uni- and multi-variate logistic regression analyses, the age (referent <50 years), history of hypertension (referent no.), hypotension process (referent ≤80 mmHg), COD (referent craniocerebral trauma), terminal eGFR(referent >60 ml·min−1·1.73 m−2), vasopressor used (Referent No), and CPR event (Referent No) were identified as independent predictors of DGF, and those variables were selected for the final scoring model. The *OR*s and confidence intervals (*CI*s) were reported for each variable as summarized in Table 3. The Hosmer–Lemeshow statistic was Chi-square = $9.05 (P = 0.422)$ for the donor risk score model, indicating that a logistic model was appropriate in the analyses. Risk scores based on the donor risk model for all predictors are shown in Table 4. The resulting donor risk score [Table 4] ranged between a minimum of 0 to a maximum of 28 points. Figure 1 depicts the frequency of DGF in both the development and validation cohorts. There was a clear increase in the incidence of DGF, moving from the low‑to‑very high‑risk score group. Based on the obtained frequencies of DGF in relation to different risk scores, we formed four risk categories of increasing severity (low risk

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Donor risk factors	Univariate analysis			Multivariate analysis		
	0R	95% CI		0R	95% CI	p
Age	1.31	$1.08 - 1.54$	0.001	1.13	$1.03 - 1.23$	0.032
History of diabetes	1.39	$1.14 - 1.66$	0.008	1.09	$1.03 - 1.26$	$0.058*$
History of hypertension	2.18	$1.21 - 3.16$	< 0.001	1.42	$1.02 - 2.06$	0.003
Hypotension process	2.72	$1.20 - 3.46$	< 0.001	1.28	$1.24 - 2.90$	0.017
Vasopressor used	1.32	$1.06 - 1.58$	0.006	1.08	$1.03 - 1.13$	0.024
Primary cause of death	1.67	$1.06 - 2.94$	0.001	1.12	$1.02 - 1.24$	0.037
Before donation eGFR	2.06	$1.12 - 3.16$	< 0.001	1.39	$1.06 - 1.82$	0.001
CPR event	1.66	$1.34 - 3.04$	< 0.001	1.47	$0.84 - 2.21$	0.001

Table 3: Donor's risk factors of DGF (development cohort, uni‑ and multi‑variate analyses)

*History of diabetes approached significance in the multivariate analysis. DGF: Delayed graft function; CPR: Cardiopulmonary resuscitation; eGFR: Estimated glomerular filtration rate; *OR*: Odds ratio; *CI*: Confidence interval.

Figure 1: The frequencies of delayed graft function in relation to different donor risk scores in development and validation cohorts. All donation after cardiac death kidney scores were no more than 18 points in both the groups. It is clear that, with the increase in donor risk score, the incidence of delayed graft function gradually increased.

0–4, moderate risk 5–9, high risk 10–14, and very high risk 15–28) to increase the number of patients in each risk category and to enhance the clinical utility of the score. The frequency of DGF across the four categories of severity in the development cohort set ranged between 4.5 and 64.5% [Figure 2]. The observed overall frequency of DGF after kidney transplantation in the development cohort was 15.2% (*n* = 55).

Validation of the predictive capacity of the scoring model

The observed overall rate of DGF after kidney transplantation in the validation cohort was 16.0% ($n = 29$). The rates of DGF in the validation cohort were close to those in the development cohort inside each of the four risk categories [Figure 2]. We did C‑statistic analysis of the two datasets, to test and compare the diagnostic accuracy of the donor risk scoring model. The C-statistic for the donor risk score in the validation cohort was 0.783 (95% *CI*: 0.680–0.886), whereas it was 0.790 (95% *CI*: 0.683–0.897) in the development cohort; the C‑statistics were not significantly different [Figure 3], indicating that the donor risk score model demonstrated good discriminative power of DGF before kidney transplantation.

Discussion

Donor organ quality has been recognized as one of the most crucial factors affecting graft function and survival in kidney transplantation. $[4,15,16]$ How to evaluate the quality of DCD kidneys has become a critical problem on kidney

transplantation field. Reduction of this complication might not only have important clinical significance, but also might bring huge economic benefits. Therefore, the pretransplant prediction model of DGF is a goal of global transplant scholars.

Kidney biopsy and histologic scores^[17,18] remain to be a gold standard for evaluating the quality of kidneys before transplantation. However, kidney biopsy is a time‑consuming and invasive process that requires experienced pathologists to assess kidney quality. Hence, several studies evaluating potential donor risk factors for allograft dysfunction and loss in kidney transplantation have highlighted the importance of the organ characteristics independent of the transplant recipient in determining allograft function and survival.^[5,7-10,15] In this study, all the listed donor risk factors [Table 2], with the exception of donor gender, BMI, ICU stay time before transplantation, and right or left kidney, were demonstrated to be predictive factors for DGF in univariate analysis. It has been reported that BMI and ICU stay time before transplantation were risk factors for DGF.^[4,6,19] These discrepancies may be due in part to our exclusion of smaller body weight (weight <30 kg) and short ICU stay time before transplantation of the donor in this study. Donor's hypotension process and CPR event were found to be significantly correlated with DGF. These findings provide novel valuable information regarding the functional relationship of these emerging risk factors. As we know,

hypotension process^[20] and CPR event^[21] can cause acute kidney injury, while acute renal injury is an independent risk factor for DGF and renal function recovery.[22‑24] The data support this connection. In the development cohort, donor variables such as age, history of hypertension, hypotension process, COD, terminal eGFR, vasopressor used, and CPR event were significantly associated with DGF multivariate analysis (history of diabetes in the borderline). Accordingly, we have established a donor risk scoring model to identify DGF at high as well as low_risk levels before transplantation [Table 4]. Furthermore, we validated the donor risk score model, which was similar to that from the development cohort (0.783 vs. 0.790, respectively), suggesting high stability of the donor risk score model.

The present study derived and validated a potential clinical prediction tool rather than a decision rule. It is to aid the attending physician who will make the clinical decision. For instance, at low– and moderate-risk categories, we recommend that the DCD kidneys can be used rest

assured. However, at high-risk categories, we recommend being cautious in the application of the DCD kidneys. Unfortunately, in very high-risk categories, we propose to abandon the application of DCD kidneys but should be based on the specific clinical situation.

Table 4: Donor score model to predict DGF in patients after kidney transplantation

DGF: Delayed graft function; CPR: Cardiopulmonary resuscitation; eGFR: Estimated glomerular filtration rate.

Figure 3: Receiver operator characteristic curves showing area under the curve for delayed graft function after kidney transplant. (a) The development cohort C‑statistic (or area under the receiver operating characteristic curve) was 0.790; (b) the validation cohort C‑statistic (or area under the receiver operating characteristic curve) was 0.783; The C‑statistics for the development cohort was similar to validation cohort.

In conclusion, we identified a pretransplantation predictive model for DGF, based on easily available donor variables. The donor risk score model might be a good noninvasive tool for evaluating the quality of DCD kidneys and potentially useful for physicians to make optimal decisions about donor organ offers.

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Conflicts of interest

There are no conflicts of interest.

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