Predictors and One-year Outcomes of Patients with Delayed Graft Function after Deceased Donor Kidney Transplantation

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Abstract

Objective:

Delayed graft function (DGF) is closely associated with the use of marginal donated kidneys due to deficits during transplantation and in recipients. We aimed to predict the incidence of DGF and evaluate its effect on graft survival.

Methods:

This retrospective study on kidney transplantation was conducted from January 1, 2018, to May 31, 2019, in the Second Xiangya Hospital of Central South University. We classified recipients into training and validation cohorts and used data from the training cohort to analyze the predictors of DGF. A nomogram was then constructed to predict the likelihood of DGF based on these predictors.

Results:

The incidence rate of DGF is 24.73%. Binary logistic regression analysis showed correlations between the incidence of DGF and cold ischemic time (CIT), warm ischemic time (WIT), donor body mass index (BMI), duration of pretransplant dialysis, diabetic donor, primary cause of donor death, and terminal serum creatinine concentration. The internal accuracy of the nomogram was 85.78%. One-year graft survival rates were 100% and 94.74%, respectively, for the groups with and without DGF ($P<0.05$).

Conclusion:

The nomogram established in this study showed good accuracy in predicting DGF after deceased donor kidney transplantation; additionally, DGF decreased one-year graft survival.

Introduction

Kidney transplantation has been successful and saved numerous lives since the 1960s. Compared to regular kidney dialysis, kidney transplantation results in better patient quality of life and longer survival [1]. Deceased donation (DD), including donation after brain death (DBD), donation after cardiac death (DCD), and donation after brain death awaiting cardiac death (DBCD), has been promoted in recent years throughout China, with increasing numbers of patients recovering from uremia. However, DGF is one of the most common postoperative complications [2, 3], the incidence of which varies from 5 to 50% in DD kidney transplantation. Because of the scarcity of donated kidneys, the use of marginal kidneys dramatically increases the incidence of DGF, which is not only a risk factor for acute rejection but is also associated with poorer long-term survival of the graft [4, 5]. Some centers believe that DGF in transplantation is a specific manifestation of acute tubular necrosis (ATN) during transplantation [6]. Generally, renal graft function recovery includes the following types: immediate graft function (IGF), slow graft function (SGF), and DGF.

Various potential factors affect the rate of DGF, including induction strategy, donor criteria, surgical process, etc. Our center utilized expanded criteria donor (ECD) kidneys to address the shortage, which was also recognized by the Organ Procurement and Transplantation Network (OPTN) in recent years [7]. Considering the contradiction between ECD and DGF, this retrospective study was conducted based on the medical records of our center to investigate the pretransplant risk factors for DGF. This study also established a visual scoring system (nomogram) model for predicting clinical outcomes to predict the incidence of DGF. Finally, we compared graft survival between the DGF and non-DGF groups.

Materials And Methods

Patients

Data on consecutive patients who had undergone kidney transplantation surgery were collected at the Second Xiangya Hospital of Central South University. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, which waived the requirement for informed consent due to the retrospective design. The inclusion criteria were (1) grafts obtained from DD, (2) surgery performed as single-kidney transplantation, (3) and only patients with complete data. Patients with a history of kidney transplantation or who had received double kidney transplants or grafts from living donors were excluded. The term ECD was used to classify subsets of all DDs over 60 years and DDs aged 50–59 years with at least two of the following characteristics: history of hypertension, serum creatinine (Scr) level above 1.5 mg/dL, and DCD [8]. Among ECDs, if possible, we used LifePort Kidney Transporters to potentially minimize preservation injury. DGF was defined as the requirement for dialysis within the first week after transplantation or a less than 25% decrease in creatinine level within the first 24 hours after surgery [9]. We further classified patients into those who did or did not experience DGF.

Eligible patients who underwent surgery between January 1 and December 31, 2018, were included in the training cohort for the development of the nomogram, while those who underwent surgery between January 1 and May 31, 2019, were included in the validation cohort.

Immunity induction therapy

Antithymocyte globulin (ATG) or interleukin 2 (IL-2) receptor blockers with steroids were used as induction therapy according to the surgeons' preferences. As some surgeons only administered steroids and drugs for cases with significant risk of infection, we classified immunity induction as "Yes" or "No" in Table 2.

Relevant variables

The DGF-related factors included donor and recipient factors. We collected donor data, including age, sex, height, weight, BMI, blood type, CIT, WIT, primary cause of death, terminal urine volume before organ harvest, terminal Scr level before organ harvest, intensive care unit (ICU) duration, hypotension history, cardiac arrest time, donation type, and history of hypertension and diabetes. The recipient indicators include sex, age, height, weight, BMI, preoperative Scr level, number of human leukocyte antigen (HLA)

mismatches, preoperative plasma renin activity (PRA) level, dialysis type, pretransplant dialysis duration, surgery duration, immunity induction history, etc.

Statistics

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 23.0. Univariate analysis was compared using unpaired, two-tailed t-tests for continuous variables while categorical variables were compared by $\chi 2$ or Fisher exact tests when data were sparse. Binary logistic regression was performed to test the impact of significant DGF-related factors in univariate analysis. P values < 0.05 were considered statistically signficant. Finally, a nomogram was developed by using version 4.0 to graphically depict the impact of significant risk factors identified in the binary logistic regression; we used the parameters of the odds ratios and β of the predictors to access the likelihood of DGF.

The internal predictive accuracy of the model was assessed among the training cohort using the area under the receiver operating characteristic curve (AUC) derived from 10-fold cross-validation by the least absolute shrinkage and selection operator (LASSO). The validation cohort was used to perform external validation by logistic analysis and calibration curves were plotted to assess the calibration of the nomogram, accompanied by Hosmer–Lemeshow tests. One-year graft survival curves were calculated using the Kaplan–Meier method and compared using log-rank tests.

Results

Patient screening

During the study period, 703 consecutive patients underwent kidney transplantation. Of these, 595 patients who met the inclusion criteria were enrolled, with 461 and 134 assigned to the training and validation cohorts, respectively (Figure S1 in the Supplement). The training cohort included 114 cases with DGF and 347 cases without DGF while the validation cohort included 41 cases with DGF and 93 cases without DGF.

Univariate analysis in the training cohort

With regard to the training cohort data, the proportion of ECD is 20.82%, and the incidence of DGF is 24.73%; ECD was significantly correlated with the occurrence of DGF($P < 0.05$). The recipients tend to be younger with just five people older than 60 years old and a median age of 37 years old. A binary logistic regression model was fitted to the remaining significant ($P < 0.05$) variables. Continuous variables (Table 1) were presented as means and standard deviations, categorical data (Table 2) were presented as proportions and percentages.

Binary logistic regression analysis

Risk factors with statistical significance in the univariate analysis were sequentially examined using binary logistic regression analysis. However, only seven factors were significantly correlated with DGF

occurrence, including donor BMI, CIT, WIT, terminal Scr, primary cause of death, history of diabetes and recipient duration of pretransplant dialysis (Table 3).

DGF risk nomogram

To visualize the results of the binary logistic regression, we used all data on the seven significant variables to develop a nomogram model, as shown in Fig. 1. One hundred points were assigned to the most effective factor (WIT) in the nomogram, followed by CIT (38 points) and donor BMI (27 points), respectively. Donor diabetes history had the least effect (13 points), while donor terminal Scr and primary cause of death had 23 and 26 points, respectively. Among recipient factors, pretransplant dialysis duration showed 19 points. Additionally, a total score of 79 corresponded to a DGF incidence of 50%.

Model validation

The nomogram model was internally validated using a cross-validation method through a LASSO binary logistic regression model (Fig. 2). The LASSO model used 10-fold cross-validation via minimum criteria and the area under. The AUC was plotted versus log(lambda); the AUC value of 85.78% indicated that the model was accurate.

External validation was performed with the validation cohort using the logistic regression formula from the training cohort. The statistic (P = 0.646) from the Hosmer–Lemeshow test showed good calibration of the DGF possibility between prediction and observation (Fig. 3). The relatively corrected C-index derived from bootstrapping validation (1,000 bootstrap resamples) for the estimation of DGF risk was 0.910 (95% confidence interval [CI], 0.855 to 0.965).

One-year graft survival follow-up

Patients from the training cohort were observed every 2 weeks during the first postoperative year. We found that 6 of 114 DGF patients experienced graft loss. The 1-year graft survival rates were 100% and 94.74%, respectively, for the groups with and without DGF. A Kaplan–Meier plot of graft survival for DGF occurrence is presented in Fig. 4; graft survival was assessed using log-rank tests (P < 0.01). Due to the limited number of graft losses (n = 6), no Cox regressions were performed.

Discussion

DGF is a common complication after kidney transplant operations and is related to both short-term functional recovery and long-term survival of kidney transplantation. Yarlagadda et al. [9] systematically reviewed the definitions of DGF, concluding that the combination of Scr reduction and dialysis need comprised a reasonable definition. Our study adopted these views as the definition allowed simple identification of DGF. Consistent with the situation in America, the number of candidates waiting for kidney transplantation is also increasing annually in China. Given the strain on kidney resources, although the utilization of ECD is associated with increased cost and DGF [8], the inclusion of ECD has

been recognized internationally. A systematic review by Tingle et al. confirmed that machine perfusion reduced the incidence of DGF [10]; thus, we used Lifeport machines for ECD kidney perfusion to address the risk as possible. In our study, ECD and DGF incidence were statistically correlated and the DGF incidence was reasonable with a proportional ECD.

The risk factors related to DGF can be divided into donor factors and recipient factors. The multiple interactions of these factors ultimately affect the recovery of graft function. Although numerous studies have assessed the causes of DGF, the results of these studies have not reached a consensus. In our study, prolonged CIT and WIT were most strongly associated with DGF, consistent with previous reports [11–18]. Additionally, longer duration of recipient pretransplant dialysis was likely to lead to DGF. Other donor predictive factors included BMI, cause of death, and terminal Scr.

While immunity induction is an important step before surgery to avoid acute rejection, the use of ATG induction remains controversial. ATG may be more likely to induce cytomegalovirus infections and hematological complications [19, 20]. Popat et al. [21] reported a lower DGF rate in the ATG-induced group among 45 patients in a single-center study. However, ATG induction did not reduce the risk of DGF in the study by de Sandes-Freitaseta's [22]. In our study, the use of ATG depended on the patient's economic condition and the surgeon's preferences since it costly; thus, this use was not predictive. The results of our study showed that donor factors were the main influencing factors of DGF, likely probably because the graft quality strongly affects renal function after transplantation. Terminal Scr is the most direct indicator of kidney quality. It is generally believed that the lower the value, the lower the incidence of DGF, as observed by Helfer [17] and in the present study.

Although long-term graft survival is expected, numerous complicated factors can cause graft loss. The relationship between DGF and deceased graft survival has been demonstrated recently [23–24]. In a 3-year DCD kidney registry analysis, Lim et al [24] reported that the recipients of DCD kidneys with DGF experienced a higher incidence of acute rejection and overall graft loss. Gill et al. [25] observed that the DGF-associated risk of graft failure was greatest in the first post-transplant year. A meta-analysis by Yarlagadda et al. verified the association between DGF, acute rejection, and graft survival. The present study performed patient follow-up in the training cohort for one year, with findings consistent with those reported by Gill et al.

Our nomogram model is a simple and visual prediction model of post-transplant factors. Maier et al. investigated the relationship between DGF and post-transplant indicators of neutrophil gelatinase-associated lipocalin (NGAL), reporting that early assessment of serum and urinary NGAL could predict DGF [26]. In their retrospective cohort study, Cardinal et al. [27] used multivariate analysis to examine the predictors of DGF but did not distinguish the importance of each predictor. Irish et al. [28] applied a scoring system for predicting DGF of DD kidney transplantation, which was verified by a ROC curve. A previous scoring system is valuable; thus, we tried to incorporate as many variables as possible to create a nomogram suitable to the condition of the contributions in our country.

The present study applied a 10-fold cross-validation LASSO method to divide the data into 10 equal parts, with nine parts for the model and one part for validation. This process was repeated ten times to produce an accurate AUC.

Our model, in addition to identifying patients at higher risk of DGF before surgery, could also be used as a clinical tool to reduce the risk of DGF. CIT should be controlled when possible; for example, shortening the harvest and patient preoperative preparation times would reduce the CIT, which would help to decrease the incidence of DGF. More specifically, this model can be used as a strategy to select suitable donors and recipients by identifying reasonable matches between recipients' conditions and CIT. Additionally, for high-risk DGF donors identified by the nomogram, the model can guide immunosuppression induction.

This study had some limitations. First was the limited sample size and data diversity since it was a single-center study. Second, the follow-up period of graft function was not long compared to 10–20 years. Finally, we did not provide solutions for predictors such as WIT. Future studies are needed to explore methods for shortening WIT and to investigate the influential factors of graft survival as prolongation of graft survival is our ultimate aim.

Conclusion

This study identified seven risk factors as predictors of DGF, including donor BMI, CIT, WIT, terminal Scr, primary cause of death, history of diabetes, and recipient duration of pretransplant dialysis. A visual nomogram with reliable accuracy was also created for clinical use.

Abbreviations

DGF: Delayed graft function

CIT: Cold ischemia time

WIT: Warm ischemia time

BMI: Body mass index

DD: Deceased donation (DD)

DBD: Donation after brain death

DCD: Donation after cardiac death

ATN: Acute tubular necrosis

IGF: Immediate graft function

SGF: Slow graft function

ECD: Expanded criteria donor

OPTN: Organ Procurement and Transplantation Network

Scr: Serum creatinine

ATG: Antithymocyte globulin

IL-2: Interleukin 2

ICU: Intensive care unit

HLA: Human leukocyte antigen

PRA: Plasma renin activity

AUC: Area under the receiver operating characteristic curve

LASSO: The Least absolute shrinkage and selection operator

CI: Confidence interval

NGAL: Neutrophil gelatinase-associated lipocalin

Declarations

Availability of data and materials

The data used in the study was extracted from our own database, and available from corresponding author on reasonable request.

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Author Contributions

Rao Chen wrote and designed the outline of the manuscript, Haifeng Wang collected data, Jianfei Hou judged DGF, Helong Dai and Longkai Peng revised the manuscript. All authors gave final approval of the version to be published.

Ethics Declarations

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. The informed consent was exempted as a retrospective study.

Disclosure of conflict of interest

None.

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Tables

Table 1

Characteristics of every continuous variable

Variables	Mean ± SD	P
Donor demographics		
Age (in years)	40.85±19.76	0.729
Donor clinical characteristics		
Weight (Kg)	59.75±19.39	0.049
Body mass index (Kg/m^2)	22.51±4.44	0.012
CIT (in hours)	12.35±3.86	0.000
WIT (in minutes)	1.94±2.08	0.000
Terminal Scr (umol/L)	82.71±49.66	0.000
Cardiac arrest time (minutes)	3.25±12.27	0.006
Terminal urine volume (ml/h)	173.43±191.23	0.152
Duration of ICU (days)	7.33±13.84	0.187
Recipient demographics		
Age (in years)	37.83±10.50	0.87
Recipient clinical characteristics		
Weight (Kg)	59.72±12.44	0.465
Body mass index (Kg/m^2)	22.02±3.66	0.548
Duration of pretransplant dialysis (months)	23.02±25.22	0.000
Pretransplant Scr (umol/L)	1029.25±349.80	0.034
HLA mismatches	4.16±1.38	0.455

Table 2
Characteristics of every categorical variable

Variables	DGF (+)	DGF (-)	P
Donor demographics			
Gender No. (%)			0.230
Male	101 (88.60)	290 (83.57)	
Female	13 (11.40)	57 (16.43)	
Donor clinical characteristics			
Donor type No. (%)			0.007
DBD	85 (74.56)	290 (83.57)	
DCD	27 (23.68)	57 (16.43)	
DBCD	2 (1.75)	0 (0)	
History of hypertension No. (%)			0.484
Yes	38 (33.33)	110 (31.70)	
No	73 (64.04)	218 (62.82)	
Unknown	3 (2.63)	19 (5.48)	
History of diabetes No. (%)			0.000
Yes	13 (11.40)	31 (8.93)	
No	77 (67.54)	295 (85.01)	
Unknown	24 (21.05)	21 (6.05)	
History of CPR			0.021
Yes	28 (24.56)	51 (14.70)	
No	86 (75.44)	296 (85.30)	
History of hypotension			0.101
Yes	74 (64.91)	194 (55.90)	
No	40 (35.09)	153 (44.09)	
Recipient demographics			
Gender No. (%)			0.128
Male	86 (75.44)	235(67.72)	
Female	28 (24.56)	112(32.28)	

Recipient clinical characteristics			
Primary cause of death No. (%)			0.000
Brain trauma	5 (4.39)	157 (45.24)	
Stoke	84 (73.68)	132 (38.04)	
Other	25 (21.92)	58 (16.71)	
Primary disease for renal failure No. (%)			0.058
Diabetes	3 (2.63)	7 (2.02)	
Hypertension	19 (16.67)	41 (11.82)	
Purpura nephritis	0 (0)	3 (0.86)	
Urologic obstruction	2 (1.75)	0 (0)	
Polycystic kidney	4 (3.51)	6 (1.73)	
Vasculitis	9 (7.89)	0 (0)	
Other	87 (76.32)	284 (82.71)	
PRA level No. (%)			0.437
Positive	6 (5.26)	22 (6.34)	
Negative	108 (94.74)	325 (93.66)	
Immunity Induction			0.421
Yes	94 (82.46)	281 (80.98)	
No	20 (17.54)	66 (19.02)	

Table 3
The results of binary logistic regression analysis

Variables	β	P Value	OR（95%CI）
Donor factors			
Weight (Kg)	1.004	0.815	1.003 (0.980-1.026)
BMI	0.101	0.041	1.107 (1.004-1.220)
CIT	0.214	0.000	1.239 (1.148-1.337)
WIT	0.433	0.000	1.542 (1.260-1.888)
Terminal Scr (umol/L)	0.006	0.043	1.006 (1.000-1.012)
Cardiac arrest time (minutes)	-0.793	0.255	0.452 (0.116-1.772)
Donation type		0.375	
DBD	18.330	0.999	91372998.68(0.000-∞)
DCD	-0.635	0.161	0.530 (0.218-1.289)
CPR history	-0.016	0.973	0.984 (0.391-2.479)
History of diabetes		0.006	
Unknown	-0.399	0.000	0.671 (0.264-1.706)
Yes	1.063	0.421	2.895 (0.864-9.697)
Primary cause of death		0.000	
Stroke	-2.911	0.000	0.054 (0.017-0.179)
Other	0.319	0.427	1.375 (0.626-3.019)
Recipient factors			
Preoperative Scr (umol/l)	0.000	0.449	1.000 (0.999-1.001)
Pretransplant dialysis duration（months）	0.012	0.049	1.012 (1.000-1.024)

β, coefficient from binary logistic regression model; OR, odds ratio; CI, confidence interval. As to categorical variables, the reference category above are DBCD, without CPR history, without diabetes, brain trauma, respectively.

Figures

Figure 1

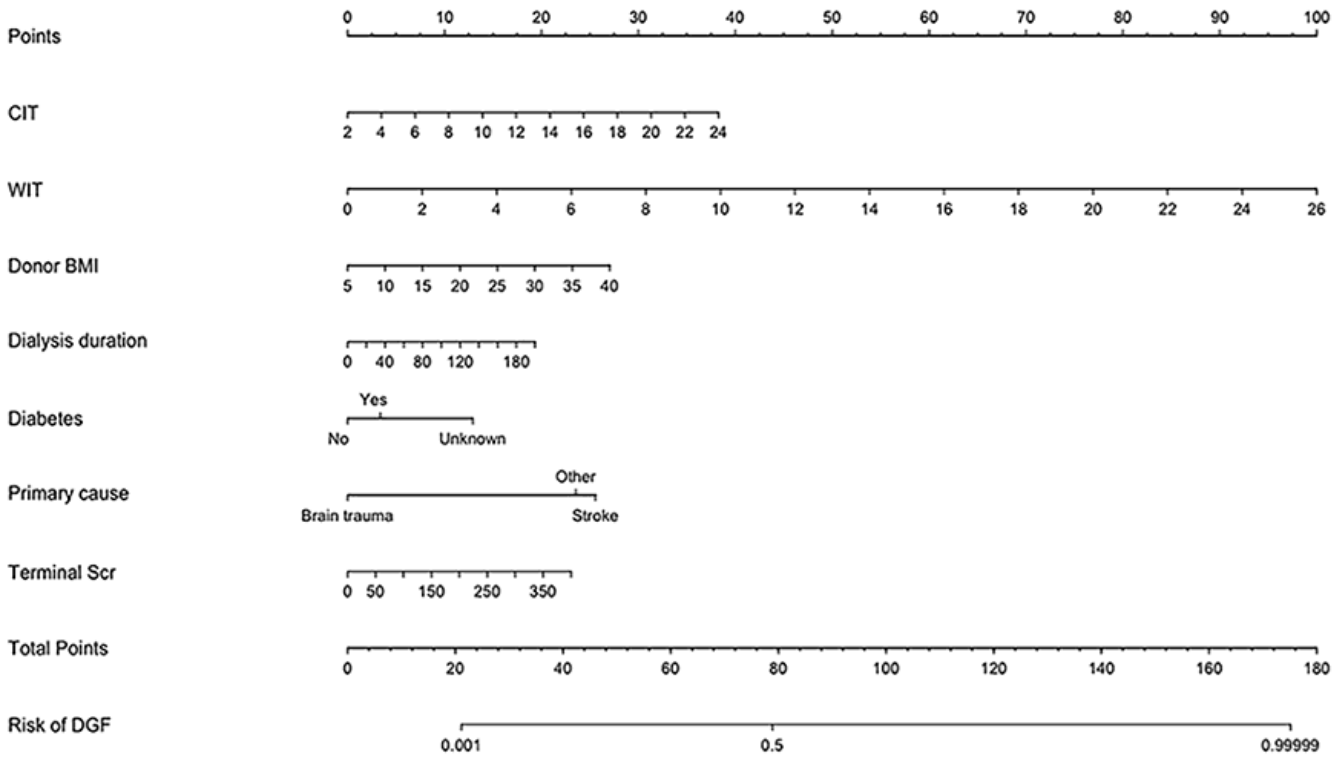

Figure 1

Nomogram of predicting the incidence of DGF.

Figure 2

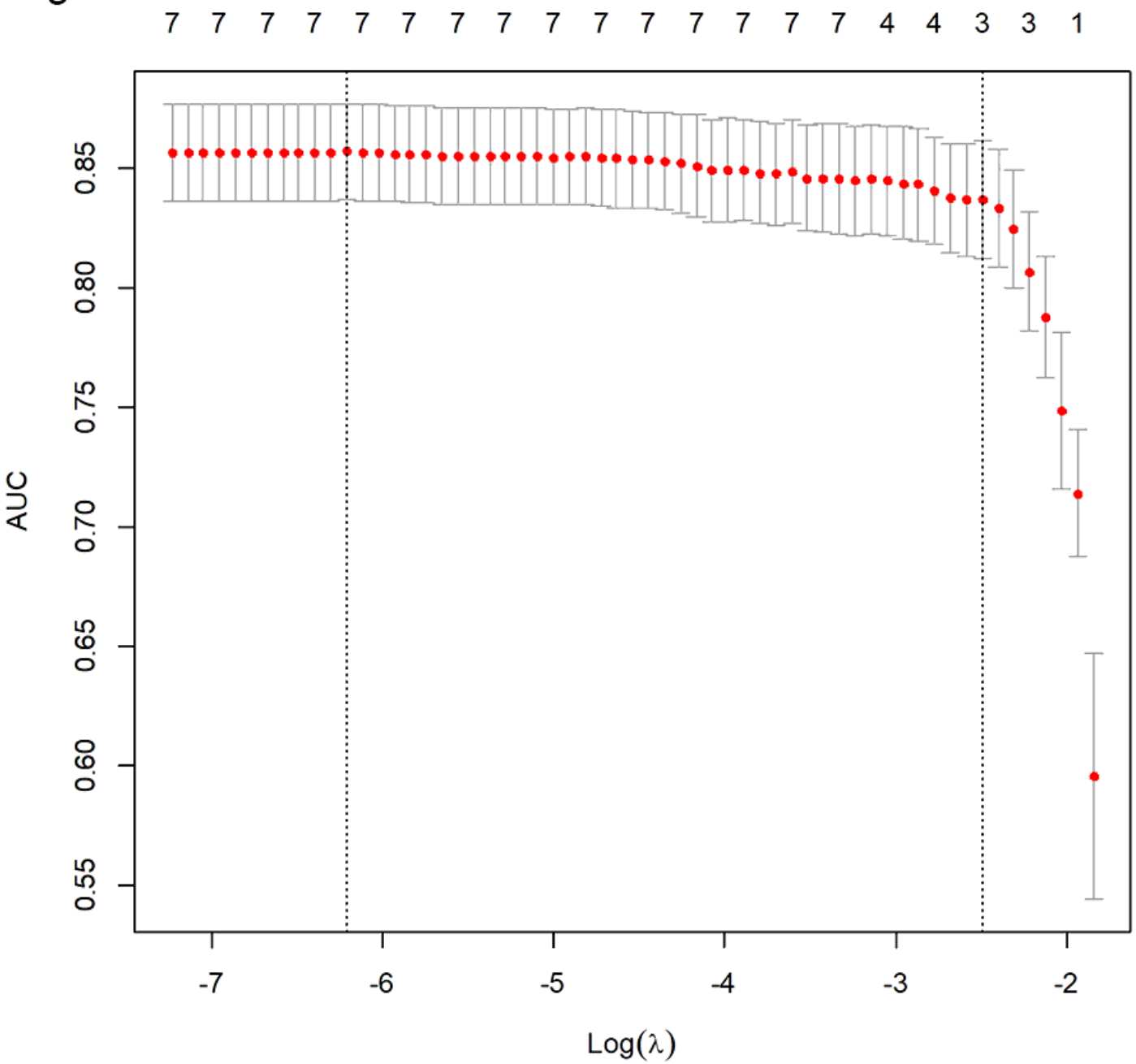

Figure 2

Internal validation: AUC plot of by LASSO. With the log (lambda) value corresponding to the minimum mean-squared error value, an AUC value produced from 10-fold cross-validation by LASSO was 85.78%

Figure 3

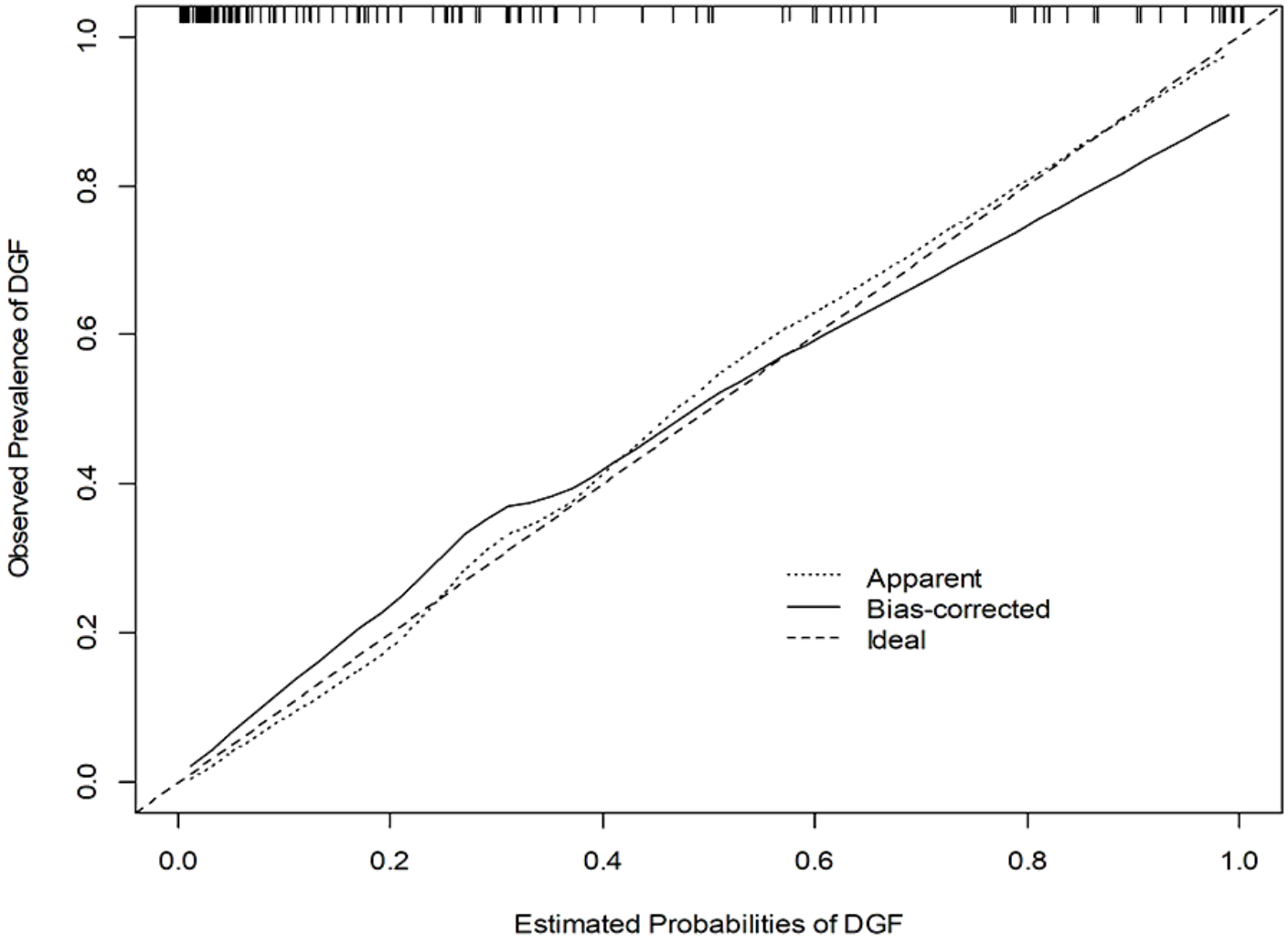

Figure 3

Calibration plot of the validation cohort. The x-axis represents the predicted DGF risk; the y-axis represents the actual DGF rate. The diagonal dashed line represents a perfect prediction by an ideal model, the dotted line represents the performance of the nomogram, and the plot shows good agreement between the predicted probabilities and the observed prevalence of DGF.

Figure 4

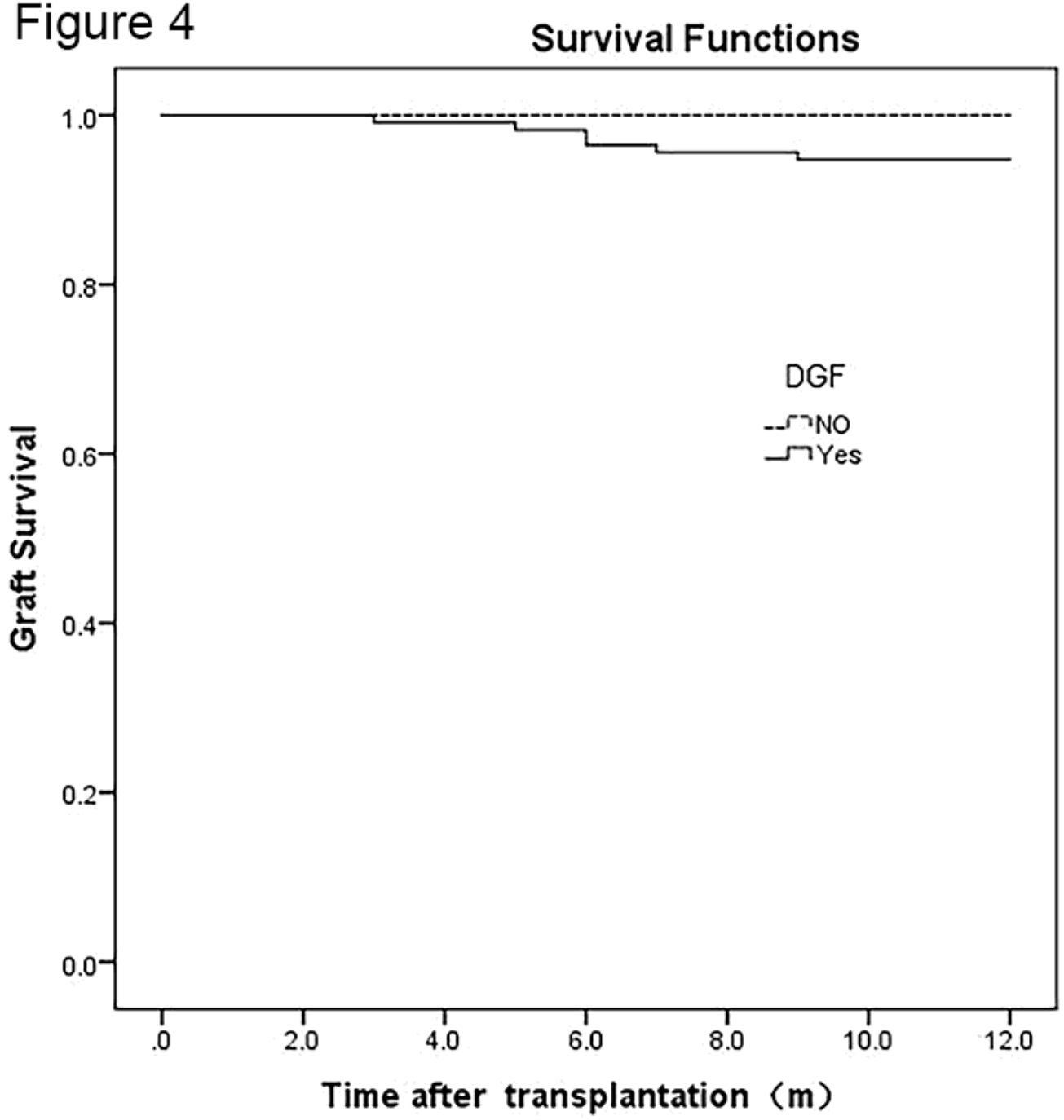

Figure 4

Kaplan–Meier plot of graft survival for DGF.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigS1.tif