Prediction of Kidney Transplant Outcome Based On Different DGF Definitions In Chinese Deceased Donation

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Abstract

Background Delayed graft function (DGF) is an important complication of kidney transplantation and can be diagnosed according to different definitions. DGF has been proven to be associated with the long-term outcome of kidney transplantation surgery. However, the best DGF definition for predicting renal transplant outcomes in Chinese donations after cardiac death (DCDs) remains to be determined. Method A total of 182 DCD kidney transplants from January 2015 to December 2015 in the First Affiliated Hospital of Xi'an Jiaotong University were diagnosed with DGF according to 6 different DGF definitions. The relationship of the DGF definitions to the three-year graft loss (GL) and 12-month estimated glomerular filtration rate (eGFR) posttransplantation was compared. Results The incidence of DGF varied from 5.01% to 50.89% according to the different DGF diagnoses. All DGF definitions were significantly associated with three-year GL and had considerable predictive power for a poorer transplant outcome. None of the DGF definitions were significantly better than the dialysis-based DGF definition. Conclusion DGF was a independent risk factor for poorer transplant outcome. In the Chinese DCD population, no definitions were superior to the universally accepted one, namely, the need for hemodialysis in the first week posttransplantation. Combination of need for hemodialysis within the first week and 48h serum creatinine reduction rate has a better predictive value for graft loss.

Background

Donation after cardiac death (DCD) has become the main source of organ transplantation in China since the use of organs from executed prisoners was forbidden in 2015[1]. Compared with the risk from other organ sources, the risk of delayed graft function (DGF) in DCD transplantation is obviously higher[2, 3].

DGF is used to describe the status of transplanted kidneys that fail to function immediately after transplantation and is an important complication of kidney transplantation. There is no consensus in the literature about how to define DGF. The straightforward United Network for Organ Sharing definition of DGF is the need for at least one dialysis treatment in the first week after transplantation (classical DGF) [4]. As reported in a previous literature[5], DGF increases the risk of chronic allograft failure and acute rejection[6, 7], which worsens allograft and patient survival[8-11].

DGF is considered to have a close relationship with ischemia-reperfusion injury (I/RI). Acute kidney injury (AKI) caused by I/RI is thought to be the most common reason an allograft fails to function immediately. The dialysis-based definition of DGF is universally accepted, but it is difficult for physicians to differentiate from other indications of dialysis and causes of early graft dysfunction, such as hyperkalemia, hyperacute rejection, acute calcineurin inhibitor toxicity, volume overload, and vascular and urinary tract complications[12, 13]. Thresholds for dialysis differ in clinicians, and the definition of DGF according to the dialysis requirement is subjective. Thus, patients may be diagnosed with DGF even though their allograft function is considerable.

The manifestation of DGF not only means a need for dialysis but also reflects the oliguresis, slowly decreased serum creatinine (sCr) and so on. There are different definitions of DGF in the literature for diagnosing DGF based on the sCr reduction ratio or urine output after surgery, which is much more objective and measurable. In 1998, Giral-Classe M et al[14] defined DGF as occurring when the time required for the kidney to reach a creatinine clearance >10 ml/min is greater than 1 week. In 2000, Boom H et al[15] proposed the definition as sCr that increases or remains unchanged or decreased<10%/day during 3 consecutive days after transplantation. In 2005, Thorne-Tjomsland G [16] defined DGF as sCr>2.5 mg/dl on Day 7 or the need for posttransplant hemodialysis. Giral-Classe M defined DGF as occurring when the time required for the kidney to reach a creatinine clearance>10 ml/min is greater than 1 week[17]. Nickerson defined DGF as failure of creatinine to decline in the first 48 h in the absence of rejection[18]. Shoskes defined DGF as urine output<75 ml/h in the first 48 h or failure of sCr to decrease by 10% in the first 48 h[19]. All definitions mentioned above were based on three essential elements, including the hemodialysis requirement, sCr and urine output posttransplant. The purpose of this study was to compare the correlation of these objective DGF definitions with transplant outcomes in Chinese DCD kidney transplants and to identify superior methods for diagnosing DGF.

Methods

Study cohort and ethics statement

For this observational cohort study, we collected data from deceased donors in a single center from January 2015 to December 2015. The study cohort was approved by the clinical research institution of the First Affiliated Hospital of Xi'an Jiaotong University and was conducted in accordance with the principles of the Declaration of Helsinki. The process of organ procurement and the transplant surgeries were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and the Red Cross Society of Shaanxi Province. We excluded recipients <16 years old and recipients of dual and en-bloc kidneys, kidneys from donors <5 years old, and multiorgan transplants. Recipients were followed up for a mean period of 1085.97±262.29 days after transplantation.

Immunosuppression and postoperative management

The basic immunosuppressive regimen used in 2015 at the First Affiliated Hospital of Xi'an Jiaotong University included cyclosporine or tacrolimus, mycophenolate mofetil (MMF), and prednisone. Rabbit antithymocyte globulin (rATG) (1.25-1.50 mg/(kg·d), intravenously) was administered for induction therapy on the day of surgery and tapered until discontinuation on postoperative day 5. Cyclosporine (6 mg/kg per day) or tacrolimus (0.06 mg/kg per day) was started with MMF (2000 mg/d) to maintain appropriate trough levels in the blood. Methylprednisolone was administered (500 mg i.v.) on the day of surgery, tapered along with the rATG and then replaced by prednisone (10 mg/d). Supplementary tapered methylprednisolone was given for three to five consecutive days when acute rejection was suspected with or without pathological evidence.

Exposure variables

We categorized recipients into different groups according to various literature-based DGF definitions, as shown in Table 1. Every day's sCr and urine output was recorded. Creatinine clearance on Day 7 posttransplant was calculated according to the MDRD equation (20, 21): [Sex*((140-Age in years)/(SCr in mg/dl))*(kg/72)], where Sex=1 for male, 0.85 for female; ignoring sCr after dialysis posttransplant.

Outcome variables

We set graft loss (GL) as a primary outcome. The current definition for GL used by the U.S. registry and regulatory bodies overseeing transplantation, including UNOS, the Scientific Registry of Transplant Recipients (SRTR) and the Centers for Medicare and Medicaid Services (CMS), encompasses a composite of both GL (return to dialysis, graft excision or retransplantation) and death[22]. We calculated the estimated glomerular filtration rate (eGFR) from clinical sCr measurements at specified time points via the Modification of Diet in Renal Disease (MDRD) Study Equation[23]. Renal function recovery time (RFRT) was defined as the number of days spent for the graft to reach sCr < 170 μmol/L. We defined graft failure as the resumption of maintenance dialysis and eGFR less than 10 ml/min/1.73 m^2.

Statistical analysis

Continuous variables are reported as the mean±SD (SD-standard deviation), and categorical variables are reported as frequencies (percentages). Twelve-month eGFR and 3-year eGFR posttransplant were compared between the DGF and non-DGF groups according to various literature-based DGF definitions using the Mann-Whitney U test. GL was assessed as primary out comes. Secondary outcomes including 12-month eGFR, and 3-year eGFR.

GL included return to dialysis, graft excision and patient death. For survival analysis, graft survival was estimated via Kaplan-Meier survival curves. The impact of various literature-based DGFs on graft survival was analyzed using the log-rank test. Multivariate Cox regression models were performed to estimate the relationship between each DGF diagnosis approach and GL after adjustment for different relevant variables, such as likelihood-ratio tests. We searched the literature for relevant donor and recipient variables associated with transplant outcomes, including donor age (years), donor hypertension history, cold ischemia time, and donor terminal sCr.

A receiver operating characteristic curve (ROC) was calculated to compare the predictive value of the clinical status based on different DGF definitions. Sensitivity, specificity, and diagnostic accuracy were calculated to further compare definitions. A two-sided P-value of 0.05 was considered statistically significant.

Statistical analysis was performed using R software.

Results

Cohort description

All recipients in our cohort received DCD organs. A flow diagram for study inclusions and exclusions is shown in Fig. 1. The study cohort consisted of 172 recipients. The mean follow-up time was 1085.97±262.29 days after transplantation. The minimum duration of follow-up was 73 days. All recipients were divided into a non-graft loss group (NGL group) and a GL group.

All recipients included were accepting kidney transplant surgery for the first time. Baseline information on the donors and recipients is summarized in Table 2. All donors and characteristics were not significantly different between these two groups except for recipient hospital stays ($P<0.001$). The mean recipient ages in the NGL group and GL group were 35.72±9.26 years and 38.48±11.46 years, respectively. Most of the recipients were male and chose hemodialysis before transplant surgery. The mean dialysis duration was 20.69±3.29 months in the NGL group and 19.96±3.22 months in the GL group, with no difference between the groups via the Mann-Whitney U test.

The mean donor age was 40.07±16.67 years in the NGL group and 36.58±20.39 years in the GL group. Eighteen donors were ≥60 years of age. Brain trauma was the most common cause of death for donors in the NGL group (51.7%) and GL group (46.2%). A history of hypertension was reported in 24.8% donors in the NGL group and 22.2% donors in the GL group. The mean cold ischemia times were 6.35±2.76 h in the NGL group and 5.63±3.18 h in the GL group (range from 2 to 13 h). A history of hypertension was reported in 24.72% of donors. The mean terminal sCr of donors before procurement was 102.67±79.29 μmol/L in the NGL group and 84.55±56.14 μmol/L in the GL group.

Incidence of DGF

Table 3 shows different DGF incidences in our cohort. Schmidt DGF, defined based on combining urine output and sCr on Day 1 posttransplant had the highest incidence of 50.89%. Giral DGF, defined based on the RFRT, had the lowest incidence of 5.01%. Classical DGF, Boom DGF, Nick DGF, Turk DGF and Shoskes DGF had DGF incidences of 20.93%, 20.24%, 10.65%, 28.94%, and 12.43% respectively.

Effect of DGF on 3-year graft outcome

GL reason distribution was disclosed in table 4, half of GL cases died with a functional allograft, only 9 of them lost the graft for chronic reason.

We examined the association between DGF and GL via multivariate Cox regression models to determine whether any specific DGF definition was able to predict graft failure more effectively. The three-year graft survival of our cohort was 84.15%. As shown in Figure 2A, graft survival for kidneys that fulfilled the definition of DGF was associated with more than 3 times the risk of GL, with a significant difference. All

DGF definitions were apparently associated with three-year GL of DCD kidneys via the Kaplan-Meier survival analysis, whereas all definitions except Nick and Giral DGF were significantly associated with death-censored GL(Figure 2B).

ROC curves were applied to examine the power of DGF for predicting graft failure in our cohort (Figure 3). As depicted in Table 5, the AUC value of all DGF definitions ranged from 0.64 to 0.81. Turk DGF was the best fit for predicting GL with the largest AUC value, whereas no definition was significantly better than classical DGF at predicting GL.

Classical DGF combined with 48h sCr reduction rate

The association of the 48 h creatinine reduction ratio with the GL was tested via the Cox proportional hazards model and calculated that the ratio was significantly correlated with the GL ($P<0.05$). Then, we added a 48 h creatinine reduction rate into the adjustment of the multivariate Cox regression and calculated an AUC value of 0.8514 (Figure 4)

Discussion

DGF is an important and intricate complication after transplant surgery. Its mechanism has not been completely understood. Previous studies have shown that DGF influences the transplant surgery outcome from DCD [24-26]. DGF is universally defined as the need for hemodialysis at 7 days posttransplant. This dialysis-based definition is subjective and has many other bases unrelated to renal function, such as hyperkalemia, volume overload, heart failure and so on[13]. This may be a possible reason why different studies of the association of DGF and graft survival have yielded opposite results. Thus, some patients with considerable graft function can be misdiagnosed with DGF. Physicians have put forward some other DGF definitions to fill that gap. This study analyzed 6 DGF definitions based on urine output, creatinine, and necessity of dialysis in the early posttransplant stage and compared their predictive power with the transplant outcome. Furthermore, the present investigation is the first to compare DGF definitions with respect to Chinese DCD transplantation.

Using retrospective cohort data for deceased-donor kidney transplant recipients, we have shown that all DGF definitions were significantly associated with three-year GL and had considerable predictive power for this outcome in the Chinese DCD cohort despite the incidence of DGF fluctuating greatly according to the definition used. DGF was associated with a more than 3-fold three-year GL. This phenomenon could be ascribed to the reduced confidence in the recovery of recipients if they suffered from DGF. In China, kidney transplant surgeries are expensive for most families, and patients usually have great expectations of transplant outcomes. DGF does not occur in China as often as it does in Western countries. Patients will suffer from tremendous psychological pressure if DGF happens, and transplant outcomes will be badly influenced. Our results were consistent with some of the previous studies[27] and contrasted with others[28]. Decruyenaere et al. [27]found that dialysis-based DGF was significantly associated with graft failure, with hazard ratios ranging from 2.87 to 13.73. However, Mallon et al. found that DGF in DCD

kidneys was not associated with inferior graft survival but that DGF was an independent risk factor in DBD cohorts. The authors ascribed this difference to the much more severe warm ischemic damage in DCD organs in the UK transplant population. Perhaps warm ischemia promotes the development of acute tubular necrosis, which was thought to be a characteristic of the delayed graft function[29, 30]. The longer the warm ischemia time (WIT) is, the severer the damage will be. In our population, there were significant differences in WIT. This may explain why DGF has a considerable predictive power for transplant outcome in DCD transplantation, in contrast to the results in other countries.

All recipients' operating curves overlapped with each other, which indicated that definitions based on objective indicators such as urine output and creatinine were not better than the classical definition.

Definitions based on urine output in our study were combined with creatinine values. These definitions corresponded with a high fluctuating DGF incidence, ranging from 12.43% to 50.89%. Using urine output-based definitions may perplex clinicians because it is not possible to differentiate urine output from the native kidney and the graft. Consequently, patients with considerable residual renal function may be misdiagnosed as not having DGF because their original kidneys have a good reaction to diuretic treatment in the early posttransplant period. Simultaneously, kidneys with severe acute tubular injury might manifest as nonoliguric renal failure, which means poor renal function companied with polyuria. In sum, urine-based DGF definitions may exhibit deviation.

The association of creatinine-based definitions of DGF or early-stage creatinine levels and changes in these levels after transplantation has been discussed many times in the previous literature[31-34]. Using creatinine-based definitions leads to bias as well. Physicians may optimize the status of recipients in whom sCr will be reduced after hemodialysis, and existing DGF may be ignored[35]. In addition, the predictive power of the three-year outcome is controversial. Boom DGF showed a considerable predictive power with an AUC of 0.797, whereas Giral DGF showed a significantly poorer predictive performance with respect to the three-year transplant outcome ($P<0.05$). Our results showed that most of the DGF definitions based on sCr had a function similar to that of the classical definition. Schnuelle et al[36] compared the creatinine-based DGF definition with the hemodialysis-based definition and found that the creatinine-based definition had a significant association with graft failure, in accordance with our results.

All DGF definitions are similar in predicting three-year GL ($P>0.05$), whereas the hazard ratio values of Nick DGF and Shoskes DGF via multivariate Cox regression were larger than that of the classical DGF, without statistical significance. The common point of these two definitions focused on the reduction rate of sCr within the 48 h posttransplant period. Creatinine-based definitions were objectively superior to the other definitions. As a result, we first tested the association of the 48 h creatinine reduction ratio with the GL via the Cox proportional hazards model and calculated that the ratio was significantly correlated with the GL ($P<0.05$). Then, we added a 48 h creatinine reduction rate into the adjustment of the multivariate Cox regression and calculated an AUC value of 0.8514 (Fig. 5), which was even greater than the original value, indicating that the combination of the need for hemodialysis within one week posttransplantation with the 48 h sCr reduction ratio has superior predictive power for GL. The combination of creatinine- and

hemodialysis-based DGF definitions can avoid the problems mentioned above and has superior operability.

Previous studies have shown that posttransplant renal function in the first year predicts long-term kidney transplant survival. The one-year posttransplant estimated glomerular rate, as the best measurement of renal function, was compared between the DGF and non-DGF groups via a Mann-Whitney U test. Three of the 6 definitions showed a significant influence on the 1-year posttransplant renal function, with no significant difference from each other. Moreover, the 12-month eGFR posttransplant was correlated with the 48 h sCr reduction ratio.

In summary, the different DGF definitions were not found to be significantly better than the classic definition based on the necessity of hemodialysis within the first week. However, the 48 h sCr reduction ratio is worth mentioning for its correlation with transplant outcomes.

Conclusion

DGF was a independent risk factor for poorer transplant outcome. In the Chinese DCD population, no definitions were superior to the universally accepted one, namely, the need for hemodialysis in the first week posttransplantation. Combination of need for hemodialysis within the first week and 48h serum creatinine reduction rate has a better predictive value for graft loss.

List Of Abbreviations

DCD

Donation after cardiac death

DGF

Delayed graft function

GL

Graft loss

NGL

No graft loss

I/RI

Ischemia-reperfusion injury

AKI

Acute kidney injury

eGFR

Estimated glomerular filtration rate

sCr

Serum creatinine

MMF

Mycophenolate mofetil

rATG

Rabbit antithymocyte globulin

RFRT

Renal function recovery time

ROC

Receiver operating characteristic curve

NGL

No graft loss

DBD

Donation after brain death

PD

Peritoneal dialysis

HD

Hemodialysis

WIT

Warm ischemia time

CIT

Cold ischemia time

AUC

Area under curve

CI

Confidence interval

Declarations

Ethic approval and consent to participate

The study had been approved by the Institutional Review Board/Ethics of The First Affiliated Hospital of Xi'an Jiao-tong University. The study has been performed in accordance with the ethical standards of the Declaration of Helsinki. All patients agreed to participate in the research and signed the information consent form.

Consent for publication

The authors agree to publication of this article in BMC Nephrology.

Availability of data and material

The data and material used and/or analyzed during the current study are available from the corresponding author.

Competing interests

The authors declare no conflict of interest.

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Author's contributions

Conception and design of study: XJH, WJX, YL;

Acquisition of data: XJH, YL, CGD, JZ;

Analysis and/or interpretation of data: XJH, YL, XMD;

Drafting the manuscript: XJH; HLX, XHT, XMP

Revising the manuscript critically for important intellectual content: WJX, PXT.

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Tables

Table 1 Literature-based DGF definitions

Definition	Time	Abbreviation
the need for at least one dialysis in the first week after Tx	·	Classical DGF
sCr increasing, remaining unchanged, or decreasing<10%/day during 3 consecutive days after Tx	2000	Boom DGF
greater than 1-week period required for the kidney to reach creatinine clearance>10 ml/min	1998	Giral DGF
failure of creatinine to decline in the first 48 h in the absence of rejection	1998	Nick DGF
urine output <75 ml/h in first 48 h or failure of sCr to decrease by 10% in the first 48 h	1995	Shoskes DGF
sCr>2.5 mg/dl on Day 7 or the need for posttransplant hemodialysis	2005	Turk DGF

Tx, transplant surgery

Table 2: Recipient and donor characteristics (study cohort)

	NGL Group	GL Group	P-value
Parameter	n=145	n=27	
Recipient characteristics			
Hospital stays (mean±SD, days)	21.49±11.41	34.08±31.47	<0.001
Age (mean±SD, years)	35.72±9.26	38.48±11.46	0.174
Male/female ratio	97/48	23/4	0.095
BMI (mean±SD, kg/m2)	20.69±3.29	19.96±3.22	0.312
ABO blood type (n,%)			
O	42(29.0%)	6(23.1%)	0.727
A	36(24.8%)	9(34.6%)	
B	51(35.2%)	9(34.6%)	
AB	16(11%)	2(7.7%)	
HLA mismatch (mean±SD)	1.59±0.95	1.72±1.06	0.544
Dialysis			
PD/HD ratio	18/120	1/22	0.206
time before Tx (mean±SD, months)	23.45±23.80	18.70±15.00	0.319
Donor characteristics			
Age (mean±SD, years)	40.07±16.67	36.58±20.39	0.344
Male/female ratio	115/30	17/9	0.192
BMI (mean±SD, kg/m2)	21.67±3.75	20.83±4.58	0.311
Cause of death (n,%)			
Trauma	75（51.7%）	12（46.2%）	0.206
Cerebrovascular disorders	55（37.9%）	8（30.8%）	
Hypoxic ischemic encephalopathy	7（4.8%）	2（7.7%）	
Tumor	2（1.4%）	0(0.0%)	
Others	6(4.1%)	4(15.4%)	
History of hypertension (n,%)	36(24.8%)	6(22.2%)	0.964
Terminal sCr (mean±SD, μmol/L)	102.67±79.29	84.55±56.14	0.266
Cold ischemia time (mean±SD, hours)	6.35±2.76	5.63±3.18	0.239

HLA, human leucocyte antigen; Tx, transplant surgery; sCr, serum creatinine; PD, peritoneal dialysis; HD, hemodialysis; aAt the time of transplantation; Continuous variables were compared via Mann-Whitney U test and categorical variable were compared via Chi-square test.

Table 3: DGF incidence

Abbreviation	Definition	Incidence
Classical DGF	the need for at least one dialysis treatment in the first week after Tx	20.93%
Boom DGF	sCr increasing, remaining unchanged or decreasing <10%/day during 3 consecutive days after Tx	20.24%
Giral DGF	greater than 1-week period required for the kidney to reach creatinine clearance>10 ml/min	5.01%
Nick DGF	failure of creatinine to decline in the first 48 h in the absence of rejection	10.65%
Shoskes DGF	urine output <75 ml/h in first 48 h or failure of sCr to decrease by 10% in the first 48 h	12.43%
Turk DGF	sCr>2.5 mg/dl on Day 7 or the need for posttransplant hemodialysis	28.94%

Table 4: Distribution of recipient GL in our cohort

Graft loss reason	**N (%)**
Patient death	
Severe pulmonary infection	8(25%)
Gastrointestinal bleeding	2(6.25%)
Multiple organ dysfunction syndrome	2(6.25%)
Cerebrovascular event	2(6.25%)
Unknown cause	1(3.12%)
Graft excision	
Rupture of graft artery	5(15.62%)
Thrombosis	2(6.25%)
Urinary tract obstruction	1(3.12%)
Chronic graft failure	9(28.12%)

Table 5 Diagnostic Accuracy of DGF definitions for three-year GL

	AUC (95% CI)	P-value
Classical DGF	0.7848(0.6722-0.8974)	-
Boom DGF	0.797(0.7029-0.891)	0.327
Giral DGF	0.6456(0.5044-0.7868)	**0.014**
Nick DGF	0.7847(0.688-0.8813)	0.425
Turk DGF	0.808(0.7085-0.9075)	0.487
Shoskes DGF	0.7959(0.6992-0.8927)	0.937

Evaluation of the predictive power of the seven DGF definitions for three-year GL by a receiver operating characteristic (ROC) curve using multivariate logistic regression models adjusting for donor age, cold ischemia time, HLA mismatch, donor hypertension history and donor terminal sCr. The P-value represents the comparison of AUC values between classical DGF and other DGF definitions via Delong's test. AUC, area under the ROC curve; CI, confidence interval

Table 6 Sensitivity, specificity and diagnostic accuracy of each definition for graft loss for recipients of DCD kidney transplants

	Sensitivity(%)	Specificity(%)	Accuracy(% [95% CI])
Classical DGF	51.8	84.8	32.3(14.8,49.7)
Giral DGF	18.2	97.1	20.8(0.2,41.7)
Nick DGF	37.5	93.8	34.9(14.5,55.3)
Turk DGF	60.9	76.5	26.4(10.3,42.4)
Shoskes DGF	45.8	93.1	41.1(21.3,60.9)
Boom DGF	50.0	84.7	29.6(11.8,47.4)

Figures

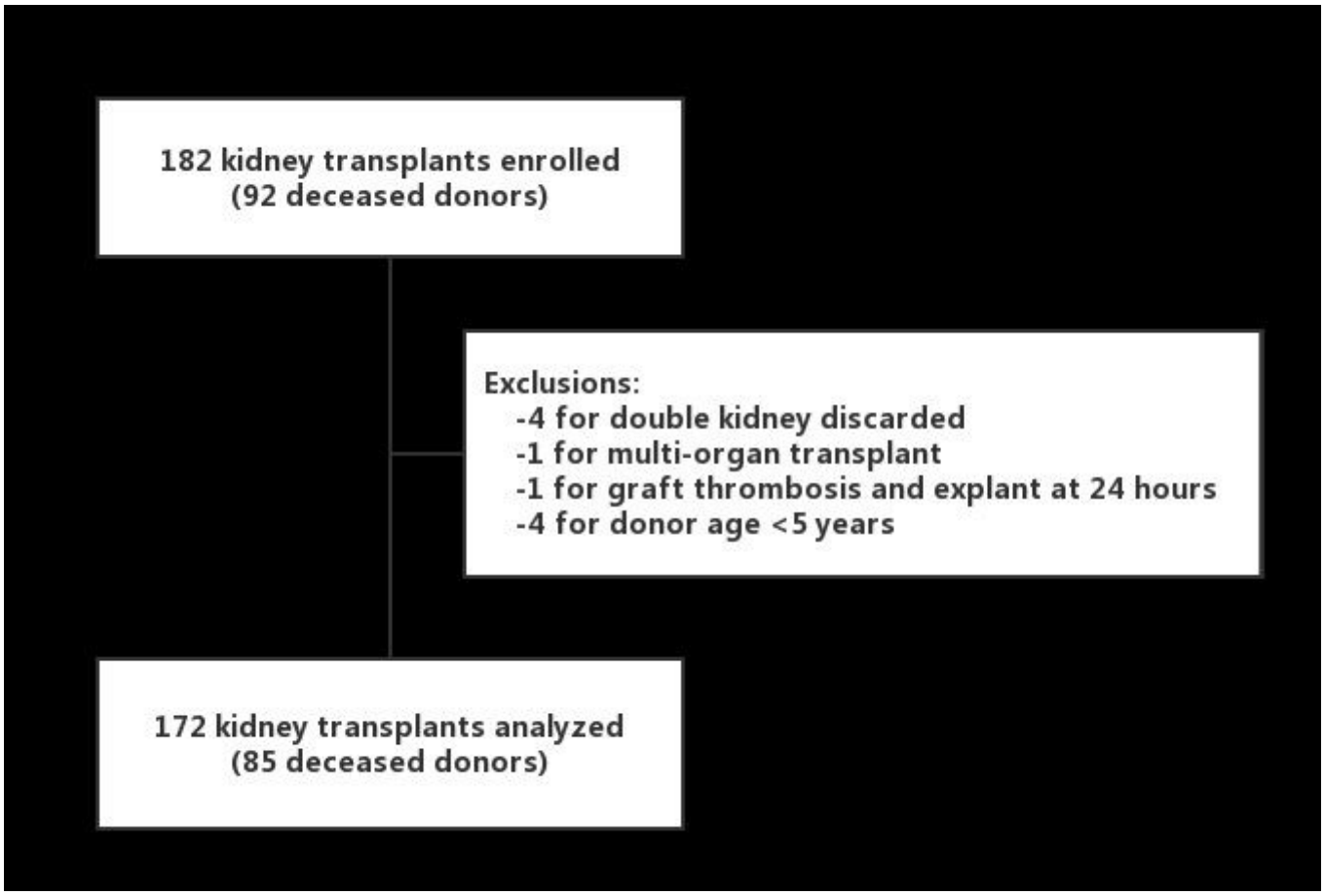

Figure 1

Study flow diagram

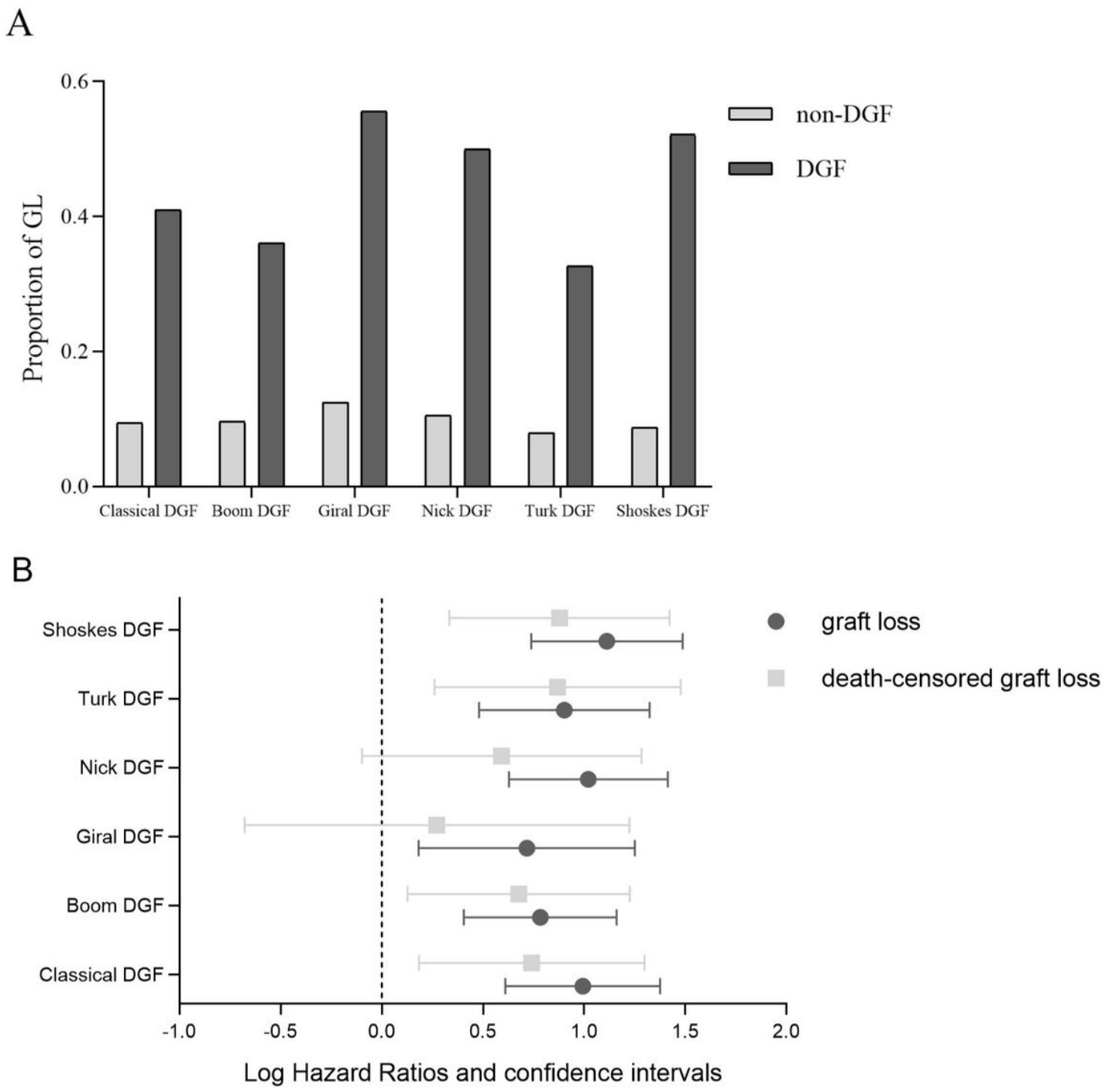

Figure 2

A. Three-year posttransplant GL proportion in the DGF cohort and non-DGF cohort. B. A multivariate Cox proportional hazards model adjusting for donor age, cold ischemia time, HLA mismatch, donor hypertension history and donor terminal sCr. The hazard ratio for GL and death-censored GL in patients with DGF compared with each other. Dots represent the logarithms of the hazard ratios. Segments represent the 95% confidence intervals.

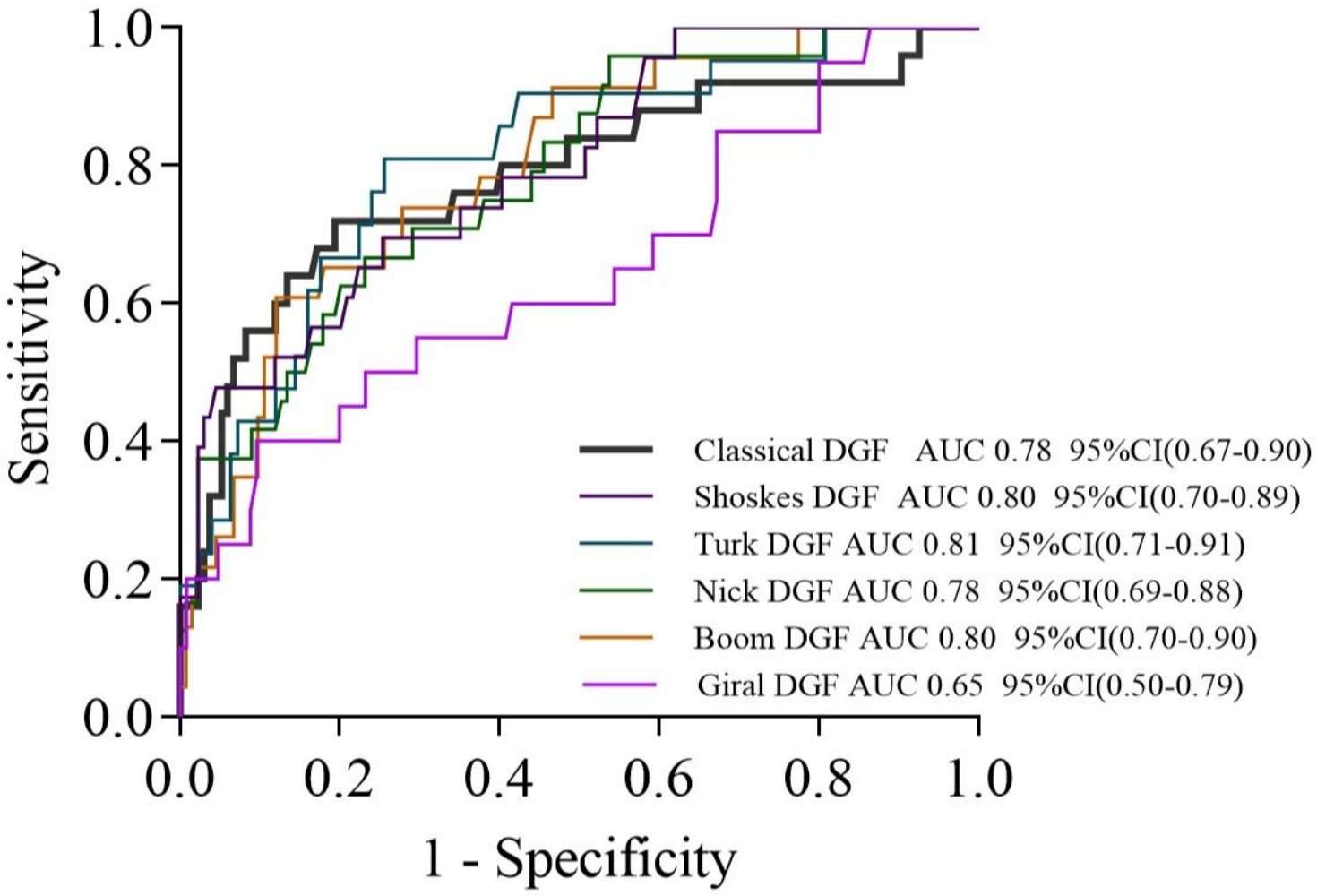

Figure 3

Evaluation of the predictive power of the seven DGF definitions for three-year GL by a receiver operating characteristic (ROC) curve using multivariate logistic regression models adjusting for donor age, cold ischemia time, HLA mismatch, donor hypertension history and donor terminal sCr.

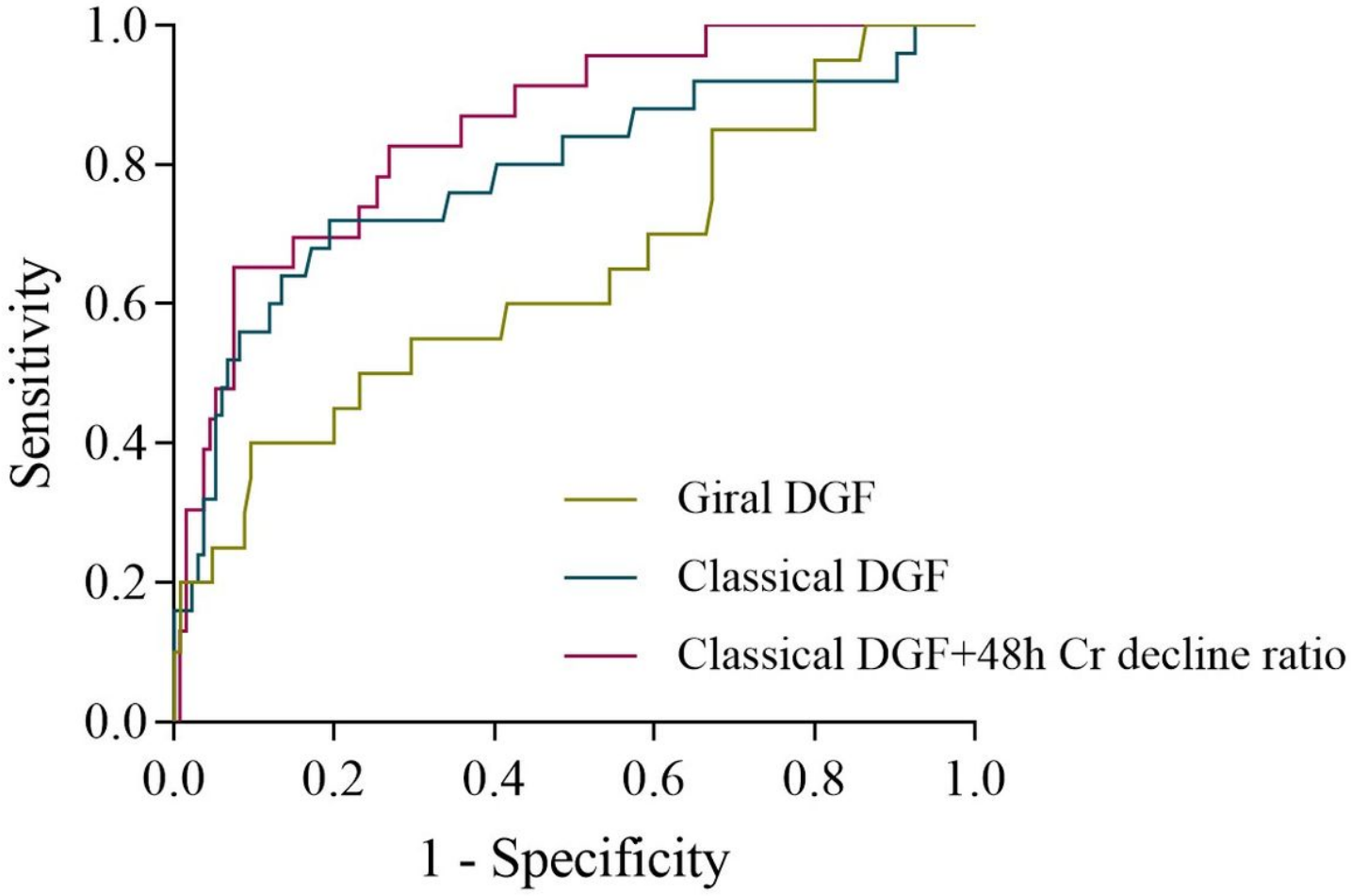

Figure 4

Evaluation of the predictive power of the classical DGF definition combined with the 48 h creatinine reduction ratio for three-year GL by a receiver operating characteristic (ROC) curve using multivariate logistic regression models adjusting for donor age, cold ischemia time, HLA mismatch, donor hypertension history and donor terminal sCr, compared with the Giral DGF definition and classical DGF definition.