Risk factors for rejection after deceased donor kidney transplantation: a mono-institutional analysis of paired kidneys

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Research

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Abstract

Background

Deceased donor kidney transplantation is an important therapeutic option for end-stage renal diseases. Adverse events including acute rejection after deceased donor kidney transplantation are not uncommon and result in poor transplant outcomes. Exploration of risk factors and patient stratification is increasingly significant to improve graft survival. This study aim to evaluate and identify the risk factors for treated rejection of patients after deceased donor kidney transplantation.

Methods

Clinical and immunological data of deceased donors and corresponding recipients between 2015 and 2018 in West China Hospital were retrospectively collected. The Kolmogorov-Smirnov test was used to indicate distribution of variables. Univariate comparisons of baseline characteristics were made with Chi-square, t and Mann-Whitney U tests. Logistic regression was constructed to analysis potential risk factors. Receiver operating characteristic curve and Jordan index were generated to determine optimal cut-off value for continuous variables.

Results

Data of 123 deceased donors and 246 recipients were obtained. The median (range) age was 41(4–62) years in recipients and 39 (1–65) years in donors. The recipients who died or suffered graft loss during the follow-up period were 8 (3.3%) and 12 (4.9%) respectively. After univariate analysis and subsequent multivariate analysis, some preoperative hemato-biochemical and transplantation-related parameters including uric acid (HR 2.132, 95%CI: 1.016–4.476, P = 0.045), platelet (HR 2.202, 95%CI:1.051–4.617, P = 0.037), absolute neutrophil count (HR 2.164, 95%CI:1.018–4.599, P = 0.045) and HLA-DQ mismatch (HR 2.197, 95%CI:1.119–4.317, P = 0.022) showed statistical significance and could be considered as independent predictors for treated rejection.

Conclusions

Including unexpected serum uric acid, several hemato-biochemical and transplantation-related parameters were found to be independent risk factors for rejection, which may contribute to stratify patients and develop personalized regimen in perioperative period.

Introduction

Worldwide, kidney transplantation from deceased donors is an important therapeutic option for patients with end-stage kidney diseases[1]. With improvement of surgical conditions and reduction of ischemic

time in recent years, the long-term survival of recipients after deceased donor kidney transplantation (DDKT) appears to be possible. Thus, researches on complications related to graft failure and mortality after organ transplantation are essential[2]. Despite some risk factors associated outcomes after DDKT have been documented before, recent evidence reveals that short-term adverse events, especially acute rejection, are still the principal reason for increased incidence of graft loss, re-transplantation and even death[3, 4]. On the other hand, it is undoubted that kidneys from deceased donors inevitably suffer various injuries in donation for many reasons[5]. It is reported that kidneys from donation after cardiac death (DCD) donors are susceptible to warm ischaemia, whilst kidneys from donation after brain-stem death (DBD) incur greater metabolic disturbance and inflammatory response[6, 7]. Thus, intricate harmful factors may limited graft survival in DDKT and require unremitting investigation[8, 9].

Actually, the association of rejection in DBD with inferior graft outcomes have been established prior to this study[6]. Meanwhile, the definition, diagnostic criteria, determination and treatment of rejection have been refined[10]. However, the outcomes of DDKT might be affected by specific allocation, health care, surgical experience and complicated risk factors related to donors and recipients, causing inevitable confounding factors and statistical bias. Thus, analysis of risk factors basing on paired donor and recipient might be conducive to reduce the bias, make correct decision on allocation and adequate preparation for recipients. Taken together, the exploration of risk factors and patients stratification are increasingly significant to improve graft survival[1]. This study aim to evaluate and identify the risk factors for treated rejection of DDKT basing on the data of paired kidneys.

Methods

Patients and data collection

We collected detailed data of both donors and recipients performed DDKT between 2015 and 2018 from the medical archives of West China Hospital. The end of follow-up period in this study is December 2020. After exclusion of 8 DDKT donors and 16 paired recipients according to exclusion criteria such as lack of major perioperative parameters, insufficient follow-up data, dual organ transplantation and donor age older than 65, we included 123 pairs and analyzed their information (Supplementary Fig. 1). Baseline characteristics included recipient profile, donor characteristics and transplantation-related features, which were showed in Tables 1–3. Recipient age were not restricted, and donor-recipient characteristics were matched correspondingly to analyze covariates better and control confounding variables. For each recipient, clinical and laboratory data within two years after transplantation were obtained.

Table 1
Baseline characteristics of recipients and their association with treated rejection.

Variables (n = 246)	Treated rejection		
	Yes	No	P-value
Gender, n(%)			0.488
Male	33 (13.4)	146 (59.3)	
Female	15 (6.1)	52 (21.1)	
Blood type, n(%)			0.235
O	20 (8.1)	61 (24.8)	
A	14 (5.7)	56 (22.8)	
B	7 (2.8)	58 (23.6)	
AB	7 (2.8)	23 (9.3)	
Primary renal disorders, n(%)			0.467
Unknown	36 (14.6)	158 (64.2)	
Glomerulonephritis-related	12 (4.9)	40 (16.3)	
Diabetes mellitus, n(%)			0.613
No	46 (18.7)	186 (75.6)	
Yes	2 (0.8)	12 (4.9)	
DGF, n(%)			0.284
No	31 (12.7)	142 (58.2)	
Yes	17 (7.0)	54 (22.1)	
Preoperative dialysis, n(%)			0.911
HD	38 (16.0)	149 (62.6)	
PD/PD combined with HD	10 (4.2)	41 (17.2)	
Previous kidney transplantation			**0.096**
No	48 (19.5)	187 (76.0)	
Yes	0 (0.0)	11 (4.5)	
Postoperative infections, n(%)			0.558
None	26 (10.6)	125 (50.8)	

Variables (n = 246)	Treated rejection		
	Yes	No	P-value
Infection			
Pulmonary	19 (7.7)	46 (18.7)	
Urinary	3 (1.2)	7 (2.8)	
Others	0 (0.0)	20 (8.1)	
Death, n(%)			0.158
Survival	48 (19.5)	190 (77.2)	
Died	0 (0.0)	8 (3.3)	
Overall graft loss, n(%)			0.318
No	47 (19.1)	187 (76.0)	
Yes	1 (0.4)	11 (4.5)	

Table 1
Continues (continuous variables)

Variables	N = 246	Association with treated rejection
Age, years(range)	41 (4–62)	0.687
BMI, kg/m^2(range)	21.5 (13.7–38.2)	**0.003**
Duration of preoperative dialysis, months(range)	24(1-240)	0.540
Preoperative laboratory workup		
Serum creatinine, μmol/L(range)	868 (254–1722)	0.119
FBG, mmol/L(range)	5.25 (3.44–27.75)	0.494
UA, μmol/L(mean ± SD)	387.5 ± 116.8	**0.004**
Hb, g/dL(mean ± SD)	113.6 ± 21.6	0.173
PLT, 10^9(range)	164 (60–401)	**0.034**
WBC, 10^9(range)	6.61 2.90-13.45)	**0.003**
ALC, 10^9(range)	1.15 (0.11–2.77)	0.544
AMC, 10^9(range)	0.33 (0.07–1.02)	0.360
ANC, 10^9(range)	4.65 (1.76–10.49)	**0.003**
NLR, ratio(range)	4.12 (1.29–67.91)	0.900
HDL, mmol/L(range)	1.25 (0.10–5.14)	0.313
LDL, mmol/L(range)	2.12 (0.36–7.94)	0.774
Triglyceride, mmol/L(range)	1.37 (0.01–108.00)	0.773

Abbreviations: BMI body mass index; HD hemodialysis; PD peritoneal dialysis; DGF delayed graft function; FBG fasting blood-glucose; UA uric acid; Hb Hemoglobin; PLT Platelet; WBC white blood cell; ALC absolute lymphocyte count; ANC absolute neutrophil count; AMC absolute monocyte count; NLR neutrophil-to-lymphocyte ratio; HDL high-density lipoprotein; LDL Low-density lipoprotein.

Bold figures indicate as statistical significance at $P < 0.10$.

Table 2
Transplantation-related features and their association with treated rejection.

Variables (n = 246)	Treated rejection		
	Yes	No	P-value
CIT			0.855
PRA I, n(%)			0.211
PRA ≤ 10%	47 (19.3)	182 (74.9)	
PRA > 10%	1 (0.4)	13 (5.3)	
PRA II, n(%)			0.576
PRA ≤ 10%	46 (18.9)	189 (77.5)	
PRA > 10%	2 (0.8)	7 (2.9)	
HLA mismatch, n(%)			
A			0.883
0	6 (2.5)	31 (12.9)	
1	30 (12.5)	121 (50.4)	
2	11 (4.6)	41 (17.1)	
B			**0.023**
0	0 (0.0)	3 (1.3)	
1	11 (4.6)	77 (32.1)	
2	36 (15.0)	113 (47.1)	
DR			0.247
0	2 (0.8)	6 (2.5)	
1	17 (7.1)	101 (42.1)	
2	28 (11.7)	86 (35.8)	
DQ			**0.028**
0	0 (0.0)	13 (6.0)	
1	22 (10.1)	103 (47.5)	
2	20 (9.2)	59 (27.2)	
Type I			0.202

Variables (n = 246)	Treated rejection		
	Yes	No	P-value
0	1 (0.4)	7 (2.8)	
1	0 (0.0)	15 (6.1)	
2	13 (5.3)	67 (27.2)	
3	27 (11.0)	79 (32.1)	
4	7 (2.8)	30 (12.2)	
Type II			**0.067**
0	1 (0.4)	9 (3.7)	
1	4 (1.6)	22 (8.9)	
2	17 (6.9)	83 (33.7)	
3	7 (2.8)	30 (12.2)	
4	19 (7.7)	54 (22.0)	
Induction, n(%)			0.722
ATG	21 (8.6)	88 (35.9)	
BSX/others	27 (11.0)	109 (44.5)	

Table 3
Baseline characteristics of donors and their association with treated rejection.

Variables	N = 246	Association with treated rejection
Age, years(range)	39 (1–65)	0.808
Gender, n(%)		0.535
Male	89 (72.4)	
Female	34 (27.6)	
Blood type, n(%)		0.505
O	46 (37.4)	
A	32 (26.0)	
B	34 (27.6)	
AB	10 (8.1)	
Diabetes mellitus, n(%)		0.494
No	115 (93.5)	
Yes	1 (0.8)	
Hypertension, n(%)		0.545
No	96 (78.0)	
Yes	25 (20.3)	
Viral hepatitis, n(%)		0.853
HBV positive	7 (5.7)	
Abbreviations: HBV hepatitis B virus; DBD donation after brain death; DCD donation after cardiac death.		
Bold figures indicate as statistical significance at P < 0.10.		

Clinical outcomes

The primary clinical outcomes was treated rejection (TR) defined as treatment for rejection within 24 months after DDKT. Meanwhile, the baseline characteristics of 123 pairs and transplantation were assessed as covariant for exploring potential risk factors. DGF was defined as receiving dialysis within 1 week following transplantation. Overall graft loss was regaining permanent dialysis after transplantation or death with functioning graft by any cause. Cold ischemic time (CIT) was defined by the time from cold storage to reperfusion following implantation. Levels of serum creatinine in recipients at preoperation and 24 months after transplantation were available for evaluation of recipient renal function and graft performance, respectively.

Statistical analysis

Statistical analyses in this study were conducted using SPSS 23.0 (SPSS Inc, Chicago, USA). The Kolmogorov-Smirnov test was used to indicate distribution of variables. Univariate comparisons of baseline characteristics between transplants suffered TR versus no rejection were made with chi-square tests, t tests and Mann-Whitney U test, as appropriate. Additionally, variables were considered as statistical significance at P values less than 0.10, which might be conducive to seek possible correlation. Logistic regression model was constructed to analysis potential risk factors. Possibly significant characteristics of recipients, paired donors and transplantation in prior correlation analyses were incorporated into regression model as covariates. Variables with statistically significance in univariate analysis were chosen into multivariate analysis. In multivariate analysis, the stepwise regression method was selected to prevent multicollinearity. Receiver operating characteristic (ROC) curve and corresponding Jordan index were generated to determine optimal cut-off value for continuous variables included regression model. In univariate and multivariate analysis, P values were two-sided and statistical significance was defined as $P < 0.05$.

Results

Characteristics of study population and their relevance with TR

Of 246 DDKT recipients, 128 (52.0%) were from donors suffered severe craniocerebral injury, 84 (34.2%) from intracranial hemorrhage and 34 (13.8%) from other diseases such as intracranial tumours. The median (range) age was 41(4–62) years in recipients and 39 (1–65) years in donors. The recipients who died or suffered graft loss during the follow-up period were 8 (3.3%) and 12 (4.9%) respectively. The median (range) body mass index (BMI) of recipients was 21.5 (13.7–38.2) Kg/m^2, which showed potential correlation with treated rejection (P = 0.003). Of transplantation-related variables, human leukocyte antigen (HLA)-B mismatch, HLA-DQ mismatch and Type II showed significant correlation with TR (P = 0.023, 0.028 and 0.067, respectively). Unexpectedly, several parameters of preoperative laboratory workup showed robust association with TR. Uric acid (UA) (P = 0.004), Platelet (P = 0.034), white blood cell (WBC) (P = 0.003) and absolute neutrophil count (ANC) (P = 0.003) showed statistical significance in association with TR. All characteristics of donors and recipients and their relevance with TR were showed in Table 1–3.

Risk factors associated with rejection

Optimal cut-off values of significant continuous variables in preliminary correlations analysis were confirmed via ROC curve and corresponding Jordan index. After that, dichotomous variables were generated and entered into univariate and multivariate analysis to explore independent risk factors. It is revealed in univariate analysis that several variables of recipients and transplantation were strongly associated with TR (Table 4). Among them, BMI (HR 3.145, 95%CI: 1.500-6.596, P = 0.002), preoperative

UA (HR 2.309, 95%CI: 1.207–4.419, P = 0.011), PLT (HR 2.519, 95%CI: 1.317–4.818, P = 0.005), WBC (HR 2.273, 95%CI: 1.193–4.330, P = 0.013) and absolute lymphocyte count (ALC) (HR 2.532, 95%CI: 1.317–4.868, P = 0.005) of recipients demonstrated potential risk for TR. Meanwhile, HLA B-mismatch (HR 2.325, 95%CI: 1.134–4.764, P = 0.021) and HLA DQ-mismatch (HR 1.950(), 95%CI: 1.057-3.600, P = 0.033) might be risk factors for TR. Previous kidney transplantation did not acquired statistical assignment, perhaps due to the small size of recipients with previous transplantation (n = 11). In the multivariate analysis, UA > 400μmol/L (HR 2.132, 95%CI: 1.016–4.476, P = 0.045), platelet (PLT) > 185*10^9 (HR 2.202, 95%CI:1.051–4.617, P = 0.037), ANC > 5.0*10^9 (HR 2.164, 95%CI:1.018–4.599, P = 0.045) and HLA-DQ mismatch (HR 2.197, 95%CI:1.119–4.317, P = 0.022) still showed statistical relevance and could be considered as independent predictors for TR (Table 4) .

Table 4
Risk factors for treated rejection in univariate and multivariate analysis.

Risk factors	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P-value	HR(95%CI)	P-value
Recipient-preoperative				
BMI > 24.5kg/m^2	3.145(1.500-6.596)	**0.002**	2.225(0.953–5.196)	0.065
Previous kidney transplantation	0.000(0.000-ns)	0.999		
UA > 400μmol/L	2.309(1.207–4.419)	**0.011**	2.132(1.016–4.476)	**0.045**
PLT > 185*10^9	2.519(1.317–4.818)	**0.005**	2.202(1.051–4.617)	**0.037**
WBC > 7.3*10^9	2.273(1.193–4.330)	**0.013**	1.748(0.832–3.672)	0.140
ANC > 5.0*10^9	2.532(1.317–4.868)	**0.005**	2.164(1.018–4.599)	**0.045**
Transplantation-related				
HLA mismatch				
B	2.325(1.134–4.764)	**0.021**	1.698(0.791–3.645)	0.174
DQ	1.950(1.057-3.600)	**0.033**	2.197(1.119–4.317)	**0.022**
Type II	1.286(0.966–1.713)	0.085		
Abbreviations: BMI body mass index; UA uric acid; PLT Platelet; WBC white blood cell; ANC absolute neutrophil count; HLA human leukocyte antigen;				
Bold figures indicate as statistical significance at P < 0.05.				

Discussion

For comprehensive analysis of outcomes from DDKT cohort, our study involved 123 donors and 246 recipients with follow-up period of 2 years at least after transplantation and detected several possible risk factors for TR. In this study, donor profiles were matched to corresponding recipients for analysis, reducing feasible selection biases in evaluation of relationship between risk factors and outcomes, and may provide pragmatic value in clinical practice.

Given the great infectious risk from over-immunosuppression caused by imbalance between immuno-suppressive protocols and occurrence of rejection, appropriate stratification of recipient is important to clinical practices. Not only could be induction regimen individually tailored for each recipient, but also immunosuppression medication be personalized basing on the profile of immunologic hazard. Hence the assessment of risk factors for rejection would be beneficial to improve graft survival and long-term prognosis of patients.

Traditionally, re-transplantation, grafts from deceased donor and high level of panel reactive antibody (PRA) have been reportedly associated with increased risk of graft loss and rejection after transplantation[11, 12]. In current cohort, these risk factors were also evaluated and none of them demonstrated significant relevance with rejection in multivariate analysis. However, apart from HLA-DQ mismatch as an independent predictor of rejection was confirmed (HR 2.197, 95%CI:1.119–4.317, P = 0.022), we also observed that several unexpected indicators from hemato-biochemical work up of recipients showed statistical relevance in regression model. Precisely, UA with cutoff value of 400μmol/L, PLT with 185*10^9 and ANC with 5.0*10^9 exhibited robust association with TR and maybe the probable risk factors for it.

Platelet, neutrophil and neutrophil-to-lymphocyte ratio (NLR) have been seemed as the surrogates for inflammatory severity which positively correlated prognosis in several diseases[13, 14]. It's speculated that these parameters or ratios could reflect the systemic inflammation which might have adverse impacts on hematologic cell lines and subsequently result in alteration of their ratios[14, 15]. Current study indicated a positive correlation of both PLT and ANC with TR (HR 2.202, 95%CI:1.051–4.617, P = 0.037 and HR 2.164, 95%CI:1.018–4.599, P = 0.045, respectively). Our hypothesis is that elevated preoperative PLT and ANC of recipients maybe represent robust inflammatory response or over-activated immune system by any cause, which may underlie the pathogenesis of rejection. Thus, for recipients with high preoperative PLT and ANC, aggressive regimen of induction and maintenance immunosuppression could be considered to decrease the risk of rejection in these patients.

Another unexpected finding in our analysis was that preoperative UA levels revealed independent association with TR. However, the comprehensive effect of UA on graft outcomes still remains controversial in published studies[16]. Although hyperuricemia could result in deterioration of renal disease by inducing endothelial dysfunction and inflammatory dysregulation, it is hard to identify that UA is a immediate cause of renal disease due to unclear causal link between elevated UA and impaired renal function[17]. It is unclear why UA could be an independent risk factor for TR in our investigation. However, to our knowledge, the association of decreased UA with reduced graft-versus-host disease (GVHD) in allogeneic stem cell transplantation (allo-SCT) has been verified by animal models, and levels of serum UA could be used as predictor for allo-SCT outcome[18]. We therefore assume that higher level of UA from reduced renal clearance might initiate non-infectious inflammation and contribute to immune reconstitution, which increased the risk of rejection. Moreover, it is not unusual that hyperuricemia would be concomitant with end-stage renal diseases. Thus, although further studies are needed to confirm our results, it is necessary to address the hyperuricemia during perioperative period.

In addition to retrospective design, this study has several inherent limitations. On one hand, despite characteristics of donors were matched to paired recipients and analysed with recipients data at once to control potential confounding variables, regression residual is an important and iterative confounding factor in observational studies. On the other hand, for the sake of reducing negative effects of multicollinearity, the stepwise method was adopted in regression model with matched donor-recipient, probably leading some variables were marginalized by those with more statistical weight. Finally, our data originated from single center, which may somewhat limit its feasibility and relevance in other settings. However, although this retrospective study based on a single-center cohort and need further validation, heterogeneity of large dataset from multi-center or even transnational registry could be significantly reduced in current analysis.

Conclusions

Our study found that several hemato-biochemical and transplantation-related parameters might be independent risk factors for treated rejection after DDKT. Actually, the exploration on these inexpensive, easily obtainable and potentially reversible indicators may contribute to stratify patients and develop personalized regimen in perioperative period for better graft outcomes. We hope our work could motivate further meta-analysis and clinical studies to provide more high-level evidence.

Declarations

Competing interests:

The authors declare no conflict of interest.

Ethics approval and consent to participate:

This article does not contain any studies with human or animal trials. This study was approved by the Institutional Ethical Committee of the West China Hospital.

Consent for publication:

All patients included in this study provided informed consent for use and publication of their data.

Abbreviations

CIT cold ischemic time; PRA panel reactive antibody; HLA human leukocyte antigen; ATG anti thymocyte globulin; BSX, basiliximab.

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Authors' contributions:

FXZ: project development, data collection, data analysis, manuscript writing; ZL: project development, data analysis; JL: data collection; KW: data collection; FZ: data collection; CW: data analysis; YX: data analysis; YL: project development, data analysis; YL:project development, data analysis; XW and TL: project development, data analysis, manuscript correction, manuscript editing.

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Abbreviations

Deceased donor kidney transplantation
DDKT; Donation after cardiac death:DCD; Donation after brain-stem death:DBD; Treated rejection:TR; Cold ischemic time:CIT; Receiver operating characteristic:ROC; White blood cell:WBC; Absolute neutrophil count:ANC; Absolute lymphocyte count:ALC; Nneutrophil-to-lymphocyte ratio:NLR; Body mass index:BMI; Uric acid:UA; Human leukocyte antigen:HLA; Platelet:PLT; Panel reactive antibody:PRA; Graft-versus-host disease:GVHD; Allogeneic stem cell transplantation:allo-SCT;

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Transplantation-related				
HLA mismatch				
B	2.325(1.134-4.764)	**0.021**	1.698(0.791-3.645)	0.174
DQ	1.950(1.057-3.600)	**0.033**	2.197(1.119-4.317)	**0.022**
Type II	1.286(0.966-1.713)	0.085		

Abbreviations: BMI body mass index; UA uric acid; PLT Platelet; WBC white blood cell; ANC absolute neutrophil count; HLA human leukocyte antigen;
Bold figures indicate as statistical significance at $P<0.05$.

Supplementary Files

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

- transplantationflowchartT.tif