De Novo Donor-specific HLA Antibodies Reduce Graft Survival and Increase Risk of Kidney Transplant Rejection: A Single-Center Retrospective Study

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Research

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Abstract

Background: This study investigated the impact of posttransplantation de novo donor-specific anti-human leukocyte antigen antibodies (dnDSAs) on long-term death-censored graft survival and renal allograft rejection.

Methods: This retrospective cohort study included 121 patients who received kidney transplants from deceased donors with negative complement-dependent cytotoxicity crossmatch. Based on the presence of dnDSAs, recipients were divided into dnDSA+ (n=31) and dnDSA- (n=90) groups. We evaluated the occurrence of rejection and long-term graft survival in the recipients along with pathologic changes in transplanted kidneys.

Results: DnDSAs were identified in 31/121 (25.6%) patients, who had lower graft survival rates than patients without dnDSAs ($P=0.007$). There was no difference in graft survival rate between patients with high (≥ 4000) and low (<4000) DSA mean fluorescence intensity ($P=0.669$). The presence of dnDSA in serum was associated with a higher incidence of antigen- and T-cell-mediated rejection ($P<0.0001$). DnDSA+ and dnDSA- groups differed in terms of Banff score for arterial fibrointimal and arteriolar hyaline thickening ($P<0.05$).

Conclusion: DnDSAs are associated with decreased long-term graft survival and increased rate of rejection, which is often accompanied by microcirculatory inflammation and positive C4d staining.

Introduction

The presence of de novo donor-specific anti-human leukocyte antigen (HLA) antibodies (dnDSA) is a well-established and important risk factor for antibody-mediated rejection and graft loss following kidney transplantation, and is associated with a higher rate of rejection and reduced graft survival [1–4]. Although advances in posttransplantation immunosuppressive regimens have reduced the incidence and effects of T-cell-mediated rejection (TCMR) and improved short-term outcomes, long-term allograft loss caused by antibody-mediated rejection (AMR) remains a major problem for kidney transplant recipients [5–6].

High DSA mean fluorescence intensity (MFI) has been linked to lower graft survival [7–9]; HLA class II DSA MFI > 5000 was an independent predictor of acute rejection in DSA+ patients [10]. Therefore, identifying the factors that contribute to immune responses and determining their association with allograft loss are critical for ensuring successful transplantation outcomes. AMR with dnDSAs is characterized by elevated expression of interferon- γ -inducible natural killer cell and T-cell transcripts and downregulation of acute kidney injury-related transcripts compared to AMR with preformed DSAs [11], which is also associated with superior graft survival. Additionally, dnDSAs are associated with biopsy-proven subclinical AMR, which leads to progressive graft injury [12].

In this study, we investigated the incidence of dnDSAs and their effects on AMR, as well as the characteristics of dnDSAs leading to AMR and long-term death-censored graft survival in renal transplant recipients.

Materials And Methods

Patients and samples

In this retrospective, single-center cohort study, we analyzed 121 patients who underwent deceased donor kidney transplantation at Tianjin First Central Hospital between January 2016 and December 2018. The inclusion criteria were as follows: (1) negative for serum HLA antibodies before transplantation; (2) age > 13 years old; (3) dnDSAs (MFI > 750) detected at any time posttransplantation; (4) underwent kidney graft biopsy with DSA detection; and (5) no specific treatment for dnDSAs received before kidney biopsy. Exclusion criteria were as follows: (1) positive panel-reactive antibody before kidney transplantation; (2) positive results for hepatitis or human immunodeficiency virus; and (3) combined multiple-organ transplantation. The study was approved by the Medical Ethics Committee of Tianjin First Central Hospital (application no. 2018N149KY). Informed, written consent was obtained from all patients and/or their guardians at the time of enrollment.

Immunosuppression

The induction regimen included paliximab (20 mg before transplantation and 20 mg on day 4 posttransplantation), or thymoglobulin (1.5 mg/kg/day) for 4 days. The immunosuppressive regimen consisted of a combination of tacrolimus (0.1 mg/kg/day) or cyclosporine (CS)A (6 mg/kg/day) and mycophenolate mofetil (1.0–1.5 g/day). The trough concentration of tacrolimus was maintained at 6–8 ng/ml for 3 months and 5–7 ng/ml at 1 year after the surgery. The trough concentration of CSA was maintained between 200–250 ng/ml for 3 months and 100–150 ng/ml at 1 year after the surgery. Hormone levels decreased rapidly after the surgery and were stable at 5 mg/day after 6 months.

HLA typing

Patients and donors were typed for HLA-A, -B, -DRB1, and -DQB1. HLA class I and II alleles were detected by PCR with a sequence-specific oligonucleotide probe using LABType SSO (One Lambda, West Hills, CA, USA). The typing information for HLA-C and -DP loci was not available for all patients and donors, and these loci were therefore not included in the analysis.

HLA antibody detection

HLA antibodies were detected using LIFECODES LifeScreen Deluxe panel-reactive antibody and Luminex Single Antigen kits (Immucor, Waukesha, WI, USA) according to the manufacturer's protocols, and analyzed using MATCH Antibody software (Immucor). Positivity or negativity was determined based on the normalized MFI calculated from negative control beads and a negative serum control. The antibody results of patients were compared with the corresponding donor's HLA to determine donor specificity. DSAs were defined based on serologic equivalence. For each patient, we recorded the number, class, specificity, and MFI of all DSAs. If a patient had more than one DSA, the MFI of the highest DSA was used.

Diagnostic criteria for rejection and delayed graft function following renal transplantation

Acute and chronic TCMR and AMR were defined by clinical and pathologic findings according to Banff 2013 criteria and Clinical Guidelines for Diagnosis and Treatment of Renal Transplant Rejection in China (2016 version) [13].

Statistical analysis

Statistical analysis was performed using SPSS v20.0 software (IBM, Armonk, NY, USA). Continuous variables are expressed as mean $\pm$ standard deviation for normally distributed data and as median with range for non-normally distributed values. Differences between groups were evaluated with the independent samples t test or χ^2 test as appropriate. The Mann–Whitney U test was used when variables showed a non-normal distribution. The cumulative incidences of TCMR, AMR, and death-censored allograft loss were assessed according to dnDSA status by Kaplan–Meier analysis. Data on graft survival were censored at the time of death. Kidney allograft survival rates were plotted as Kaplan–Meier curves and compared between the 2 groups with the log-rank test. P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Pretransplantation clinical characteristics of the 121 recipients and their donors are listed in Table 1. The median age of both recipients and donors was 44 years. The majority of recipients (71.1%) and donors (90.1%) were male. The median follow-up period was 34 months (range: 12–51 months). The median number of HLA-A, -B, -DRB1, and -DQB1 mismatches was 6.

Table 1
Patient characteristics

Characteristic	
Number of patients	121
Recipient age at transplantation (years)	44 (13–70)
Recipient, male (%)	86 (71.1%)
Donor age at transplantation (years)	44 (2–68)
Donor, male (%)	109 (90.1%)
HLA serotype mismatch	
Class I and II	5.49 ± 1.91
A	1.16 ± 0.78
B	1.58 ± 0.58
DR	1.48 ± 0.66
DQ	1.27 ± 0.70
panel-reactive antibody at pre-transplantation	0 (0%)
ABO blood type incompatibility (%)	0 (0%)
Second transplantation (%)	2 (1.65%)
Pretransplantation diabetes	26 (21.5%)
Follow-up period (months)	34 (12–51)
HLA, human leukocyte antigen	

Comparison of clinical characteristics between dnDSA + and dnDSA – patients

There were no significant differences in recipient and donor characteristics between patients with and those without dnDSAs. Pretransplantation comorbidities were similar between the 2 groups. Average HLA serotype mismatching at the A and DQ loci also showed no differences between groups, but mismatches at the DR and DQ loci were higher in patients with dnDSAs than in those without dnDSAs (Table 2).

Table 2
Clinical characteristics of de novo DSA – and de novo DSA + patients

Characteristic	De novo DSA+ (n = 31)	De novo DSA– (n = 90)	P value
Recipient characteristics at transplantation			
Age, years (mean ± SD)	47.6 ± 13.4	42.5 ± 12.3	0.496
Male sex, n (%)	24 (77.4%)	62 (68.9%)	0.366
Donor characteristics at transplantation			
Age, years (mean ± SD)	40.4 ± 19.3	43.0 ± 14.5	0.002
Male sex, n (%)	30 (96.8%)	79 (87.8%)	0.148
HLA serotype mismatch			
Class I and II	6.56 ± 1.50	5.19 ± 1.91	0.135
A	1.48 ± 0.71	1.07 ± 0.78	0.962
B	1.72 ± 0.54	1.54 ± 0.59	0.046
DR	1.84 ± 0.47	1.38 ± 0.67	< 0.0001
DQ	1.52 ± 0.71	1.20 ± 0.68	0.490
Transplantation characteristics and treatment at transplantation and at follow-up			
Pretransplantation comorbidities, n (%)			
Diabetes	14 (45.2%)	12 (13.3%)	0.0002
Hypertension	28 (90.3%)	82 (91.1%)	0.895
Renal anemia	29 (93.5%)	85 (94.4%)	0.854
Repeat transplantation, n (%)	2 (6.5%)	0 (0%)	–
Cold ischemia time(h),mean ± SD	5.35 ± 1.36	4.79 ± 1.93	0.125
Renal biochemical test for de novo DSA			
sCr (μmol/l)	237.02 ± 238.1	131.4 ± 113.6	< 0.0001
Induction therapy,n(%)	30(96.8%)	84(93.3%)	
Thymoglobulin	12(38.7%)	5(5.6%)	< 0.0001
Basiliximab	17(54.8%)	79(87.8%)	0.0002
Thymoglobulin + Basiliximab	1(3.2%)	0	/
Immunosuppressive regimen, n (%)			
CsA, cyclosporine A; DSA, donor-specific HLA antigen; FK506, tacrolimus; HLA, human leukocyte antigen; MMF, mycophenolate-mofetil; Pred, prednisone; sCr, serum creatinine; SD, standard deviation			

Characteristic	De novo DSA+ (n = 31)	De novo DSA- (n = 90)	P value
CsA + MMF + Pred	7 (22.6%)	7 (7.8%)	0.026
FK506 + MMF + Pred	24 (77.4%)	83 (92.2%)	
Follow-up (months)	27.3 ± 12.0	34.1 ± 10.5	0.499
CsA, cyclosporine A; DSA, donor-specific HLA antigen; FK506, tacrolimus; HLA, human leukocyte antigen; MMF, mycophenolate-mofetil; Pred, prednisone; sCr, serum creatinine; SD, standard deviation			

Frequency distribution of dnDSAs in kidney transplant recipients

We observed that 31/121 (25.6%) patients developed dnDSAs after kidney transplantation, including against HLA class I antigens (4/31, 12.9%), HLA class II antigens (22/31, 71.0%), and both classes of HLA antigen (5/31, 16.1%). Additionally, 14/31 (45.2%) patients developed only 1 DSA, 9/31 (20%) developed 2, and 8/31 (25.8%) developed ≥ 3 . The average time of DSA generation was 10 months (range: 1–38 months). Table 3 shows the frequency distribution of dnDSAs by HLA class and locus. Most dnDSAs were generated against the DQ locus. The locus specificity of dnDSAs was as follows: A, 9/31 (29.0%); B, 2/31 (6.5%); DRB1, 12/31 (38.7%); and DQ, 24/31 (77.4%). There were significant differences in the incidence of dnDSAs between DQ mismatch groups ($P = 0.009$; Fig. 1).

Table 3
Frequency of de novo DSA by HLA class and locus

All patients (n = 121)	
DSA+, n (%)	31 (25.6%)
By HLA class	
DSA class I, n (%)	4 (12.9%)
DSA class II, n (%)	22 (71.0%)
DSA class I + II, n (%)	5 (16.1%)
By HLA locus	
HLA-A, n (%)	9 (29.0%)
HLA-B, n (%)	2 (6.5%)
HLA-DRB1, n (%)	12 (38.7%)
HLA-DQB1, n (%)	24 (77.4%)
DSA, donor-specific HLA antigen; HLA, human leukocyte antigen	

Treatment and outcome of kidney recipients

Of the 121 kidney transplant cases, 27 (22.3%) were classified as rejection, as determined by pathologic biopsy. There were 13 (41.9%) and 14 (15.6%) cases of rejection in the dnDSA + and dnDSA – groups, respectively.

We analyzed the cumulative hazards of AMR, TCMR, and AMR + TCMR in the 2 patient groups according to their posttransplantation serum dnDSA status (Fig. 2A–C). Patients with serum dnDSAs had a higher incidence of AMR ($P < 0.0001$; Fig. 2A) and a higher cumulative hazard of AMR + TCMR ($P < 0.0001$; Fig. 2B) than those without dnDSAs. The cumulative hazard of TCMR was similar between the 2 patients groups ($P = 0.441$; Fig. 2C).

TCMR was observed in 14 patients in the dnDSA – group; this was reversed in 12 cases, while posttreatment renal allograft failure occurred in 2 cases. Of the 13 cases classified as rejection in the dnDSA + group, 4 (30.8%) were AMR, 2 (15.4%) were TCMR, and 7 (53.8%) were a combination of AMR and TCMR. Following treatment, 3 cases of AMR were reversed and 1 was considered as renal allograft failure; 5 cases of AMR + TCMR were reversed and 2 constituted renal allograft failure; and 2 cases of TCMR were reversed. TCMR was mainly treated by hormone shock and antithymoglobulin, while AMR was treated with intravenous immunoglobulin, plasmapheresis, and rituximab. After active treatment, 24/27 recipients with rejection had stable renal function and 3 had loss of function of the grafted kidney.

Posttransplantation dnDSAs and occurrence of AMR

Patients with posttransplantation dnDSAs were stratified into 2 groups according to the presence or absence of AMR alone or in combination with TCMR to evaluate the influence of different variables on transplantation outcome. There were no statistically significant differences between the patient groups for any of the analyzed variables (Table 4).

Table 4

Distribution of variables in patients with dnDSA stratified according to presence or absence of AMR

Variable	dnDSAs with AMR (n = 11)	dnDSAs without AMR (n = 20)	P value
Recipient			
Age, years (mean $\pm$ SD)	46.82 $\pm$ 15.08	47.95 $\pm$ 12.73	0.652
Male sex, n (%)	9 (81.8)	15 (75.0)	0.664
Type of HLA molecules, n (%)			
A	3 (27.3)	6 (30.0)	0.873
B	0(0)	2 (10.0)	0.278
DR	6 (54.5)	6 (30.0)	0.180
DQ	7 (63.6)	17 (85.0)	0.174
Immunosuppression, n (%)			
CsA + MMF + Pred	4 (36.4)	3 (15.0)	0.174
FK506 + MMF + Pred	7 (63.6)	17 (85.0)	–
CDC-PRA > 10%, n (%)	0 (0)	0 (0)	–
HLA-mismatch A/B, n (%)			
0–2	4 (36.4)	5 (25.0)	0.505
3–4	7 (63.6)	15 (75.0)	0.505
HLA-mismatch DR/DQ, n (%)			
0–2	4 (36.4)	4 (20)	0.319
3–4	7 (63.6)	16 (80)	0.319
Average MFI of dnDSA			
A	6426.7 $\pm$ 5130.6	1713.0 $\pm$ 491.1	0.006
B	0	1671.0 $\pm$ 742.5	/
DR	7594.0 $\pm$ 7762.8	4453.6 $\pm$ 555.3	0.236
DQ	11689.5 $\pm$ 5803.9	5349.0 $\pm$ 4015.6	0.432
Pretransplantation diabetes, n (%)	8 (72.7)	6 (30.0)	0.022

AMR, antibody-mediated rejection; CDC-PRA, complement-dependent cytotoxicity panel-reactive antibody; CsA, cyclosporine A; dnDSA, de novo donor-specific HLA antigen; FK506, tacrolimus; HLA, human leukocyte antigen; MMF, mycophenolate-mofetil; Pred, prednisone; SD, standard deviation; TCMR, T-cell-mediated rejection

Variable	dnDSAs with AMR (n = 11)	dnDSAs without AMR (n = 20)	P value
Donors			
Age, years (mean $\pm$ SD)	31.09 $\pm$ 20.48	45.50 $\pm$ 17.07	0.839
Male sex, n (%)	10 (90.9)	20 (100)	0.171
AMR, antibody-mediated rejection; CDC-PRA, complement-dependent cytotoxicity panel-reactive antibody; CsA, cyclosporine A; dnDSA, de novo donor-specific HLA antigen; FK506, tacrolimus; HLA, human leukocyte antigen; MMF, mycophenolate-mofetil; Pred, prednisone; SD, standard deviation; TCMR, T-cell-mediated rejection			

DnDSAs and long-term graft survival

We investigated the effect of dnDSAs on graft survival and found that the survival rate was lower in patients with dnDSAs than in those without dnDSAs ($P = 0.007$; Fig. 3). There was no difference in graft survival rates between patients with a high MFI level (≥ 4000) and those with a low level (< 4000) ($P = 0.669$; Fig. 4).

Banff score

There were significant differences between the dnDSA+ and dnDSA- groups in terms of arterial fibrointimal thickening and arteriolar hyaline thickening, but no differences in microvascular inflammation (peritubular capillary and glomerular inflammation), microvascular injury (chronic glomerulitis and mesangial basal thickening), arterial endocarditis, and scar lesions (interstitial fibrosis and renal tubule atrophy) (Table 5).

Table 5
Banff score of renal allografts in recipients with rejection in each group

Group	n	ptc	g	mm	cg	v	ci	cv	ct	i	t	aah
dnDSA+	13	1.31 $\pm$ 0.86	0.38 $\pm$ 0.65	0	0	0.08 $\pm$ 0.28	0.23 $\pm$ 0.60	0	0.15 $\pm$ 0.56	1.77 $\pm$ 0.73	2 $\pm$ 0.71	0
dnDSA-	14	0.71 $\pm$ 0.73	0.29 $\pm$ 0.47	0	0	0.07 $\pm$ 0.27	0.29 $\pm$ 0.47	0.07 $\pm$ 0.27	0.36 $\pm$ 0.84	2.07 $\pm$ 0.62	1.86 $\pm$ 0.54	0.21 $\pm$ 0.58
P value		0.339	0.25	-	-	0.92	0.89	0.047	0.20	0.25	0.59	0.01
Banff score categories: aah, arteriolar hyaline thickening; cg, transplant glomerulopathy; ci, interstitial fibrosis; ct, tubular atrophy; cv, arterial fibrointimal thickening; g, glomerulitis; i, interstitial inflammation; mm, mesangial matrix increase; ptc, peritubular capillary inflammation; t, tubulitis; v, vascular inflammation.												

Discussion

Donor-specific antibodies binding to HLA on the donor endothelium can activate a cascade of events leading to graft injury, such as leukocyte recruitment; endothelial cell activation through complement activation, which induces a proinflammatory and prothrombotic phenotype or endothelial cell lysis in the case of high lytic membrane attack complex levels; and antibody-dependent cellular cytotoxicity [14, 15]. Over the past decades, research on factors affecting the outcome of kidney transplantation has shifted from T-cell-mediated processes, calcineurin inhibitor toxicity, and chronic allograft nephropathy to the humoral rejection that is primarily responsible for allograft loss, which has prompted investigations into posttransplantation development of anti-HLA antibodies and DSAs. In this study, we found that dnDSAs occurred in 25.6% of patients after transplantation. Of these, 71% were against HLA class II antigens, which was higher than the rate for HLA class I; and the DQ locus specificity of dnDSAs was 77.4%. The higher abundance of dnDSAs against class II as compared to class I is consistent with findings from other solid organs [16–18], although the underlying cause remains unclear.

The influence of dnDSA characteristics on clinical outcomes is controversial. Previous studies reported that high DSA MFI levels were associated with poorer graft outcomes [7–9]. In this study, there was no significant difference in graft survival rates between patients with a high DSA MFI level (≥ 4000) and those with a low level (< 4000). HLA class II DSA MFI > 5000 was shown to be an independent predictor of acute rejection in DSA+ patients [10]; our small sample size may have precluded the observation of a similar trend.

The presence of dnDSAs increased the probability of rejection episodes (AMR or TCMR or both). Patients who were dnDSA+ had an elevated risk of experiencing a rejection episode, which was the cause of early graft loss. Among dnDSA- patients, those without anti-HLA antibodies had the lowest risk of rejection, which was more likely to be TCMR; the higher graft survival rates in this group could therefore be related to better control of this type of rejection with immunosuppressive therapy.

It is unclear why only some patients with serum DSAs had AMR episodes and why those who did not showed stable renal function following transplantation. This could not be explained by the analyzed variables nor by stratifying patients with DSAs according to their AMR status. Although our analysis was limited by the small number of patients, our findings are in accordance with previous reports [19]. IgG subtype (fixing or nonfixing complement), false positives in the Luminex assay, low levels of antibodies that do not damage the organ, and the accommodation phenomenon in transplanted solid organs [20, 21] could explain the rejection observed in patients with anti-HLA DSAs. Additionally, there may be differences at the HLA locus against which the antibodies are directed (eg, HLA-DQ), but a statistical analysis to evaluate this possibility was not possible because of the small number of patients in our study with antibodies against a single locus.

Another important issue faced by transplant physicians is the detection of dnDSAs associated with adverse events, given the variable pathogenicity of dnDSAs. Although the complement-binding capacity of DSAs is a critical factor influencing DSA pathogenicity [22, 23], this cannot be readily assessed in clinical practice. We therefore examined the characteristics of dnDSAs resulting in AMR and found that contrary to our expectation, they were not extremely detrimental based on their numbers and average MFI values,

which were indistinguishable from those of silent dnDSAs. This may be explained by the prozone effect, which refers to false-negative results arising from factors that interfere with the binding of the secondary detection reagent [24] such as high antibody titers leading to complement activation and deposition of C1 complexes on beads, IgM antibodies, or other serum factors [24]. We speculate that actual dnDSA titers leading to AMR in this study were higher than measured values. The lack of differences in DSA characteristics between kidney transplant recipients with and those without AMR may be attributable to the small number of patients with DSAs leading to AMR. However, given that the higher average MFI of DSAs against HLA-DQ showed a trend of increased risk of developing of AMR, clinicians should be aware of the risk of formation of high-affinity DSAs against HLA-DQ, and increase the intensity of immunosuppressive therapy accordingly in order to prevent opportunistic infections.

To determine the contribution of circulating dnDSAs to graft injury, the correlation between DSAs in peripheral blood and histopathologic lesions in renal allografts was evaluated. MFI sum score of renal allografts was shown to be associated with immune activation in peripheral blood [25], and the presence of dnDSAs has been linked to microvascular lesions or peritubular capillaritis [26] but not to scarring lesions [27–28]. Contrary to previous evidence, we did not find any pathologic correlations with dnDSAs; there was no significant association between MFI sum score and the number and MFI of DSAs, which could be explained by the fewer episodes of acute rejection in our study population.

Our study had several limitations. Firstly, as it was a single-center study with a retrospective design, the sample size was relatively small. Secondly, we did not perform complement-binding assays such as binding to C1q or C3d, which could have yielded results that were more informative. Thirdly, a longer follow-up time is needed to compare allograft survival according to the presence of dnDSAs. Finally, the lack of complete donor and recipient HLA-C and -DP typing information prevented a comprehensive analysis of DSAs for all potential HLA loci, as these 2 loci have been linked to graft rejection [29, 30].

In conclusion, we evaluated the impact of posttransplantation dnDSAs on long-term death-censored graft survival and rejection in patients who received a kidney allograft with pretransplantation-negative CDC crossmatch. Graft survival rates were lower in patients with dnDSAs than in those without DSAs. Thus, posttransplantation DSAs can predict long-term outcomes for renal transplantation, although further study is needed to determine whether periodic DSA monitoring and characterization can improve the rate of success.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Tianjin First Central Hospital (application number 2018N149KY).

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no conflicts of interest.

Found

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Authors' contributions

DHL conceived the study. WL performed the experiments, analyzed the data, and drafted the manuscript. ZYK and LY collected the data and revised the manuscript draft. YLX and CL performed DSA measurements and HLA typing. JZ screened the clinical data. All authors discussed the results and reviewed the manuscript.

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Figures

Figure 1

Cumulative incidence for different numbers of DQ mismatch.

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Cumulative incidence for different numbers of DQ mismatch.

Figure 2

Cumulative hazard of rejection episodes in dnDSA- and dnDSA+ groups. A: Cumulative hazard of AMR alone. B: Cumulative hazard of TCMR+AMR. C: Cumulative hazard of TCMR alone.

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Cumulative hazard of rejection episodes in dnDSA- and dnDSA+ groups. A: Cumulative hazard of AMR alone. B: Cumulative hazard of TCMR+AMR. C: Cumulative hazard of TCMR alone.

Figure 3

Death-censored graft survival rates of patients with and without dnDSA.

Figure 3

Death-censored graft survival rates of patients with and without dnDSA.

Figure 4

Death-censored graft survival rates in patients with high (≥ 4000) and low (< 4000) DSA MFI levels.

Figure 4

Death-censored graft survival rates in patients with high (≥ 4000) and low (< 4000) DSA MFI levels.