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Effect of HLA-C and DQ matching on Pediatric Heart Transplant Graft Survival

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Abstract

Background—Higher degree of HLA matching at the A, B, and DR-loci has been associated with improved long-term survival after pediatric heart transplantation in multiple ISHLT registry reports. The aim of this study was to investigate the association of HLA matching at the C and DQ loci with pediatric graft survival.

Methods—The UNOS database was queried for isolated heart transplants that occurred from 1988 to 2012 with a recipient age of 17 or less and at least one postoperative follow up encounter. When analyzing HLA matching at the C or DQ loci, only those transplants with complete typing of donor and recipient at the respective loci were included. Transplants were divided into patients with at least one match at the C-locus (C-match) versus no match (C-no), and at least one match at the DQ locus versus no match (DQ-match versus DQ-no). Primary outcome was graft loss. Univariate analysis was performed with log-rank test. Cox regression analysis was performed with following patient factors included in the model: recipient age, ischemic time; recipient on ventilator, ECMO, ventricular assist device or inotropes at transplant; recipient serum bilirubin

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and creatinine closest to transplant, donor-recipient weight ratio, underlying cardiac diagnosis, crossmatch results, transplant year, and HLA matching at the A, B, and DR loci.

Results—Complete typing at the C-locus occurred in 2429/4731 (51%) transplants and 3498/4731 (74%) transplants had complete typing at the DQ locus. C-match did not differ from C-no with respect to patient factors, except for year of transplant; [C-match median year 2007 (IQR 1997–2010) vs. C-no median year 2005 (IQR 1996–2009), $p=0.03$] and degree of HLA matching at A, B, and DR loci (11.9% of C-match with high level of HLA matching v. 3% of C-no, $p<0.01$). Matching at the C-locus was not associated with decreased risk of graft loss [C-no median graft survival 13.1 yrs (95%CI 11.5–14.8) vs. C-match 15.1 yrs (95%CI 13.5–16.6) $p=0.44$, log-rank, hazard ratio 0.93 (95%CI 0.76–1.15, $p=0.52$)]. DQ-match did not differ from DQ-no in any of the above-mentioned patient factors, except DQ-match was more likely to have high degree of matching at the A, B, and DR loci versus DQ-no (9.8% v. 3.2%, $p<0.01$). Matching at the DQ-locus was not associated with decreased risk of graft loss [DQ-no median graft survival 13.1 yrs (95%CI 11.7–14.6) vs. DQ-match 13.0 yrs (11.4–14.6) $p=0.80$, log rank, hazard ratio 0.95 (0.81–1.1), $p=0.51$].

Conclusion—Complete typing at the C-locus of both donor and recipient occurs less often than typing at the DQ locus. A higher degree of donor-recipient HLA matching at the C-locus or the DQ-locus appears not to confer any graft survival advantage.

Introduction

HLA typing of potential donors and recipients is standard of care in pediatric heart transplantation. Investigations into the effect of HLA matching on graft survival in heart transplantation have shown improved graft survival and outcomes with increasing levels of HLA matching.^{1–4} Until recently the effect of HLA matching in pediatric heart transplantation has remained relatively unexplored. Despite an early study showing no correlation between HLA matching on graft outcomes, recent reports utilizing large multi-institutional databases show that increasing HLA matching is associated with improved graft survival.^{5–8}

Previous investigations on HLA matching in heart transplantation have concentrated on matching at the HLA-A, B and DR-loci. Recently, typing at the HLA-C and DQ loci have been utilized in solid organ transplant. HLA-C plays a vital role in the activity of natural killer cells.⁹ HLA-C matching has been associated with better outcomes in stem cell transplantation, renal, and liver transplantation.^{10–12} The effect of HLA-C matching has remained relatively unexplored in heart transplantation. HLA-DQ locus is present on antigen presenting cells and is involved in presenting self and foreign proteins to the immune system. HLA-DQ matching has not been associated with improved outcomes in renal or liver transplantation, and there are conflicting reports on its effect in bone marrow transplantation.^{10, 13–15}

The aim of this study was to investigate the effect of matching at the HLA-C and DQ loci on graft survival in pediatric heart transplantation.

Methods

A retrospective analysis was performed on data obtained from the UNOS Standard Transplant Analysis and Research (STAR) files. The Medical University of South Carolina Institutional Review Board approved the study. Heart transplants performed in the United States between October 1, 1987 through December 31, 2012 were included for analysis. The database was queried for pediatric heart transplants (age 17 or younger) who underwent heart transplant. Transplants were included if there was at least one follow-up visit documented. Transplants were excluded if complete typing of the donor and/or recipient with respect to the specific loci (HLA-C or DQ) of interest was not reported.

Transplants were divided into those who had at least one or more matches at the loci of interest versus no match (C-no v. C-match; DQ-no v. DQ-match). The primary endpoint was graft loss, which included patient death or retransplantation. Patient characteristics compared between groups included: recipient supported by inotropic medications, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD) and/or mechanical ventilation immediately prior to transplant; cardiac diagnosis (cardiomyopathy, congenital heart disease, retransplant or other), recipient age, serum creatinine and bilirubin at transplant, ischemic time, donor-recipient weight ratio, crossmatch results, and year of transplant. When controlling for HLA matching at the A, B and DR loci, transplants were divided into three groups, no HLA matching [0 of 6 potential matches (HLA-no)], low level of HLA matching [1–2 of 6 potential matches (HLA-low)] and high level of HLA matching [3–6 potential matches (HLA-high)]. These variables were chosen as they have been previously been shown to be associated with graft survival.^{5, 16, 17}

Secondary endpoints included the development of coronary vasculopathy over the life of the graft and rejection requiring treatment in the first post-transplant year. In order to allow for at least one year for the assessment of rejection or the development coronary vasculopathy, only transplants prior to December 31, 2011 were included for analysis of the secondary endpoints.

Statistical Analysis

Data from the UNOS STAR files were imported into SPSS®, version 21.0 (IBM® Armonk, NY) for analysis. Demographic and patient variable data are reported as medians with interquartile ranges, or ninety-five percent confidence interval, or as percentages as appropriate. Demographic and patient variable data were compared between HLA donor-recipient matching groups using Wilcoxon-rank sum test for continuous variables and chi-square tests for categorical variables. Graft survival was compared using log rank test.

Cox proportional hazard models were used to assess hazard ratios of graft loss between HLA match groups while controlling for age, year of transplant; recipient on ECMO, VAD, intravenous inotropes or mechanical ventilation immediately prior to transplant, cardiac diagnosis, serum bilirubin and creatinine, donor-recipient weight ratio, pro- or retrospective crossmatch results, and HLA matching at the A, B, and DR loci. For the purpose of the multivariate Cox-regression analysis, continuous variables of transplant year and age were divided to create categorical variables: early transplant year (1987–1999) versus late

transplant year (2000–2012); infant (<1 year of age), child (1–10 years) and adolescent (11–17 years). Positive and indeterminate retrospective crossmatches were combined into one category for multivariate analysis. Only data sets with complete data were used in the Cox proportional hazard models; missing data was not imputed. No match at the HLA locus of interest (HLA-C-no and HLA-DQ-no) was the reference group in multivariable analysis.

To assess whether the additional information added from matching at the C or DQ locus could improve the Cox-regression model performance, a Cox-regression “R²” was computed. The formula is as follows: $R^2 = 1 - e^{-(LRT/n)}$, where LRT = difference in -2 log likelihood between the null model and model with covariates.¹⁸ A Cox-regression model was created using before described covariates, specifically HLA matching at the A, B, and DR loci was categorized as no, low and high as previously outlined. A second Cox-regression model was then created with the only change in covariates being HLA matching incorporating matching at A, B, DR and C loci. For this model, HLA groups were classified as no (0 matches), low (1–3 matches), high (4–8 matches). This process was repeated for the DQ loci. Lastly this process was repeated for transplants which had complete typing at both the C and DQ loci. In this analysis, HLA matching groups were defined as no (0 matches), low (1–4 matches), high (5–10 matches). P-values <0.05 were considered to be statistically significant.

Results

There were 4731 transplants in 4526 patients who met study inclusion criteria. Complete typing of the donor and recipient at the HLA-C locus occurred in 2429 (51%) transplants, and complete typing at HLA-DQ locus occurred in 3498 (74%) transplants. Characteristics of the C-locus cohort and DQ-locus cohort are described in Table 1 and 2.

The C-no cohort (n=1528) did not differ from C-match (n=901) in terms of recipient age, serum creatinine and bilirubin, donor-recipient weight ratio, ischemic time, positive or indeterminate crossmatch, underlying cardiac diagnosis, recipient on ECMO, VAD, mechanical ventilation or inotropes (Table 1). Median transplant year was later for C-match (2007, IQR 1997–2010) v. C-no (2005, IQR 1996–2009), $p < 0.01$. C-match was more likely to have a high level of matching at A, B, and DR loci (n=107, 11.9%) than C-no (n=46, 3%, $p < 0.01$)

C-no had a median graft survival of 13.1 years (95%CI 11.5–14.8yrs) with 94% survival at 1 year post-transplant, 76% at 5 years, 57% at 10 years, 44% at 15 years and 29% at 20 years, versus C-match median graft survival of 15.1 years (95%CI 13.5–16.6yrs, $p = 0.44$, log-rank test)(Figure 1) with 94% survival at 1 year, 75% at 5 years, 61% at 10 years, 50% at 15 years and 31% at 20 years. In multivariable Cox-regression analysis, there was no difference in graft loss between C-no and C-match, hazard ratio for C-match versus C-no 0.93 (95%CI 0.76–1.15, $p = 0.52$). Over the life of the graft, C-no had similar reported frequency of transplant coronary vasculopathy than C-match [19.6% (n=301) v. 17.9% (n=161), respectively, $p = 0.27$]. C-no and C-match had similar rates of treated rejection in the first post-transplant year (C-no 21.8%, n=333 v. C-match 22.2%, n=200, $p = 0.11$).

DQ-no (n=1837) did not differ from DQ-match (n=1661) with respect to any patient factors mentioned before (Table 2), other than DQ-match was more likely to have a high level of matching at A,B, and DR (n=106, 9.8%) versus DQ-no (n=36, 3.2%, $p<0.01$). There was no difference in graft survival between DQ-no (median 13.1yrs, 95% CI 11.7–14.6yrs; 93% at 1 year, 76% at 5 years, 57% at 10 years, 45% at 15 years, 30% at 20 years) versus DQ-match (median 13.0yrs, 95% CI 11.4–14.6; 94% at 1 year, 75% at 5 years, 58% at 10 years, 45% at 15 years and 34% at 20 years; $p=0.80$, log-rank test)(figure 2). In multivariable cox regression analysis when controlling for other covariates, DQ matching remained not associated with graft loss (DQ-match vs. DQ-no HR=0.95, 95% CI 0.81–1.11, $p=0.51$).

The DQ-match group was more likely to have reported coronary vasculopathy over the life of the graft (20.8%, n=383) than the DQ-no group (23.9%, n=397, $p=0.03$). Due to the univariate association between matching at the DQ locus and coronary vasculopathy, multivariable logistic regression was performed controlling for previously mentioned patient variables. In logistic regression analysis DQ matching was not independently associated with reported coronary vasculopathy ($p=0.81$). In addition, DQ-match did not have a statistically lower rate of treated rejection within the first post-transplant year (n=344, 21%) compared to DQ-no (n=426, 23%, $p=0.21$).

In the cohort of patients with C locus typing, Cox-regression multivariable R^2 was 0.11, when HLA classification only considered matching at the A, B and DR loci (3 matches, n=153). When Cox-regression model considered matching at the A, B, DR and C loci (4 matches, n=175), the R^2 did not improve ($R^2=0.11$). In the cohort of patient DQ locus typing, Cox-regression model R^2 was 0.10 when HLA only considered matching at the A, B and DR loci (3 matches, n=221). When matching at the A, B, DR and DQ loci were considered (4 matches, n=276), the Cox-regression model R^2 remained at 0.10. There were 1589 transplants who had complete typing of donor and recipient at both the C and DQ loci. In this cohort, when HLA matching was defined only by A, B, and DR loci (3 matches, n=142), the Cox-regression model R^2 was 0.09. When HLA matching was defined by A, B, C, DR and DQ loci (5 matches, n= 164), the Cox-regression model R^2 was also 0.09.

Discussion

To the authors' knowledge, this report represents the first ever investigation of matching at HLA-C and DQ loci in adult or pediatric heart transplantation. Previous investigations have been limited to analyzing the A, B and DR loci.^{5, 8} Our investigation showed no association between donor-recipient matching at the C and DQ loci and graft survival, rejection within the first transplant year or reported transplant coronary vasculopathy.

HLA-C and DQ play important roles in the immune system, and these loci have a biological role in the post-transplant course.¹⁹ However, their lack of association with graft survival is likely from a combination of two factors. First, there is significant association between HLA haplotypes. HLA haplotypes are conserved as all HLA alleles are encoded on the same chromosome. This is evidenced in the current study by matching at C and DQ being highly associated with matching at the A, B, and DR loci in this study. Therefore, matching at HLA A, B, and DR is co-linear with matching at HLA-C and/or DQ. This can bias the cox-

regression model against finding significant associations at the C and DQ locus. Second, there is a relatively low hazard ratio associated with HLA matching at A, B, and DR in previous pediatric heart transplant studies.^{5, 8} Given the relatively small improvement in survival associated with matching at the HLA-A, B, and DR loci and higher impact of other patient characteristics, the current study may be underpowered to detect differences in graft survival between HLA-C and DQ matching cohorts.^{5, 8} Future studies in matching at the C and DQ locus should be done on larger multi-institutional databases, such as the ISHLT database. However, given the current analysis, it appears that matching at the C and DQ loci does not add any additional information above matching at the A, B, and DR loci.

In bone marrow transplantation, matching at C-locus was associated with improved survival, in part by reducing the incidence of graft-versus host disease.¹⁰ HLA-C matching is associated with lower rates of rejection in liver and renal transplants, however, its association with graft survival has yet to be established.^{11, 12} Our study found no association between graft survival or early reported rejection in HLA-C matching. Similar to other reports in solid organ transplant and bone marrow transplant, our study did not find associations between HLA matching at the DQ locus and graft outcomes or early rejection.^{10, 13–15}

Both C and DQ play an important role in the immune system, and antibodies against each loci have been associated with the development of post-transplant antibody-mediated rejection in solid organ transplants.^{19–21} Due to limitations of the database, the authors were not able to investigate specifically the incidence of antibody-mediated rejection or rejection beyond the first year. In a single center study, the development of antibody-mediated rejection was associated with higher incidence of cardiovascular mortality and the development of coronary vasculopathy in pediatric heart transplant recipients.²² In an analysis of 103 pediatric heart transplants, antibody-mediated rejection was associated increased rates of graft failure and mortality.²³ Though, it is still possible that the incidence of late antibody-mediated rejection is different between the matching groups at either loci but did not lead to a change in graft survival.

Matching at the class II HLA-DR loci has been associated with lower rates of coronary vasculopathy in adult heart transplantation.⁴ Previous analysis of the UNOS database found no association between HLA-A, B, or DR matching and freedom from coronary vasculopathy in pediatric heart transplant recipients.²⁴ While DQ is as Class II HLA antigen, there was no association between DQ matching and freedom from coronary vasculopathy. In fact, matching at DQ locus was associated with higher frequency of coronary vasculopathy in univariate analysis, however, this association did not persist when controlling for patient factors, including year of transplant.

Limitations

The influence on HLA-C and DQ matching in donor evaluation by transplant centers is not known, therefore, the distribution of HLA-C and DQ matching may not represent actual random chance but be influenced by decision making processes not accounted for. There was no set definition of transplant coronary vasculopathy or rejection within the first year and therefore reporting of this information was solely left to the discrimination of the

reporting institution. The methods and frequency of surveillance for transplant coronary vasculopathy are not known and could have varied greatly between institutions influencing the reporting of coronary vasculopathy. The database is dependent upon accurate reporting from participating institutions. The type of rejection, cellular versus antibody-mediated versus mixed, was not reported in the database and therefore limited the authors' ability to discern associations between HLA-C and DQ matching and frequency of specific types of rejection, such as antibody-mediated rejection. A lack of consistent late reporting of rejection in the database prevented the authors from assessing associations between HLA matching and late rejection.

Conclusion

Complete typing at the C-locus of both donor and recipient occurs less often than typing at the DQ locus. A higher degree of donor-recipient HLA matching at the C-locus or the DQ-locus appears not to confer any graft survival advantage.

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References

- Opelz G, Wujciak T. The influence of HLA compatibility on graft survival after heart transplantation. The Collaborative Transplant Study. *N Engl J Med*. 1994 Mar 24; 330(12):816–819. [PubMed: 8068075]
- Opelz G, Wujciak T, Dohler B, Scherer S, Mytilineos J. HLA compatibility and organ transplant survival. Collaborative Transplant Study. *Rev Immunogenet*. 1999; 1(3):334–342. [PubMed: 11256424]
- Kilic A, Weiss ES, Allen JG, et al. Simple score to assess the risk of rejection after orthotopic heart transplantation. *Circulation*. 2012 Jun 19; 125(24):3013–3021. [PubMed: 22634267]
- Kaczmarek I, Deutsch MA, Rohrer ME, et al. HLA-DR matching improves survival after heart transplantation: is it time to change allocation policies? *J Heart Lung Transplant*. 2006 Sep; 25(9):1057–1062. [PubMed: 16962466]
- Dipchand AI, Kirk R, Edwards LB, et al. The registry of the international society for heart and lung transplantation: sixteenth official pediatric heart transplantation report-2013; focus theme: age. *J Heart Lung Transplant*. 2013 Oct; 32(10):979–988. [PubMed: 24054806]
- Kirk R, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report-- 2012. *J Heart Lung Transplant*. 2012 Oct; 31(10):1065–1072. [PubMed: 22975096]
- Alonso de Begona J, Gundry SR, Nehlsen-Cannarella SL, et al. HLA matching and its effect on infant and pediatric cardiac graft survival. The Loma Linda Pediatric Cardiac Transplant Team. *Transplant Proc*. 1991 Feb; 23(1 Pt 2):1139–1141. [PubMed: 1989171]
- Butts RJ, Scheurer MA, Atz AM, et al. Association of Human Leukocyte Antigen Donor-Recipient Matching and Pediatric Heart Transplant Graft Survival. *Circ Heart Fail*. 2014 May 15.

9. Ljunggren HG, Oudshoorn-Snoek M, Masucci MG, Ploegh HL. High-resolution onedimensional isoelectric focusing of mouse MHC class I antigens. Identification of natural and experimentally induced class I antigens. *Immunogenetics*. 1990; 32(6):440–450. [PubMed: 2272666]
10. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. *Blood*. 2004 Oct 1; 104(7):1923–1930. [PubMed: 15191952]
11. Lopez-Alvarez MR, Moya-Quiles MR, Minguela A, et al. HLA-C matching and liver transplants: donor-recipient genotypes influence early outcome and CD8+KIR2D+ T-cells recuperation. *Transplantation*. 2009 Aug 15; 88(3 Suppl):S54–S61. [PubMed: 19667963]
12. Frohn C, Fricke L, Puchta JC, Kirchner H. The effect of HLA-C matching on acute renal transplant rejection. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2001 Feb; 16(2):355–360.
13. Freedman BI, Thacker LR, Heise ER, Adams PL. HLA-DQ matching in cadaveric renal transplantation. *Clinical transplantation*. 1997 Oct; 11(5 Pt 2):480–484. [PubMed: 9361945]
14. Gajewski J, Gjertson D, Cecka M, et al. The impact of T-cell depletion on the effects of HLA DR beta 1 and DQ beta allele matching in HLA serologically identical unrelated donor bone marrow transplantation. *Biol Blood Marrow Transplant*. 1997 Jun; 3(2):76–82. [PubMed: 9267667]
15. Campos J, Quijano Y, Franco A, et al. Beneficial effects of HLA class II incompatibility in living donor liver transplantation. *Transplant Proc*. 2003 Aug; 35(5):1888–1891. [PubMed: 12962835]
16. Benden C, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric lung and heart-lung transplantation report--2012. *J Heart Lung Transplant*. 2012 Oct; 31(10):1087–1095. [PubMed: 22975098]
17. Mahle WT, Kanter KR, Vincent RN. Disparities in outcome for black patients after pediatric heart transplantation. *J Pediatr*. 2005 Dec; 147(6):739–743. [PubMed: 16356422]
18. Hosmer, D.; Lemeshow, S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*. New York: John Wiley and Sons Inc; 1999.
19. Ticehurst EH, Molina MR, Frank R, et al. Antibody-mediated rejection in heart transplant patients: long-term follow up of patients with high levels of donor-directed anti-DQ antibodies. *Clin Transpl*. 2011;409–414. [PubMed: 22755439]
20. Bosch A, Llorente S, Eguia J, et al. HLA-C antibodies are associated with irreversible rejection in kidney transplantation: Shared molecular epitopes characterization. *Hum Immunol*. 2014 Jan 30.
21. Bachelet T, Couzi L, Guidicelli G, et al. Anti-Cw donor-specific alloantibodies can lead to positive flow cytometry crossmatch and irreversible acute antibody-mediated rejection. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2011 Jul; 11(7):1543–1544.
22. Everitt MD, Hammond ME, Snow GL, et al. Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant. *J Heart Lung Transplant*. 2012 Jul; 31(7):686–693. [PubMed: 22551931]
23. Casarez TW, Perens G, Williams RJ, et al. Humoral rejection in pediatric orthotopic heart transplantation. *J Heart Lung Transplant*. 2007 Feb; 26(2):114–119. [PubMed: 17258143]
24. Kobayashi D, Du W, L'Ecuyer T. Predictors of cardiac allograft vasculopathy in pediatric heart transplant recipients. *Pediatric transplantation*. 2013 Aug; 17(5):436–440. [PubMed: 23714284]

Number at Risk

C-no	620	296	128	24
C-match	326	161	77	11

Figure 1.

Kaplan-Meier curve depicting graft survival between transplants with a match at HLA-C locus versus those with no match. Number at risk for each cohort at 5, 10, 15 and 20 years post-transplant are shown below the curve. There was no difference in graft survival. HLA-C-no: 13.1 years (95% CI 11.5–14.8yrs) versus HLA-C-match: 15.1 years (95% CI 13.5–16.6yrs, $p=0.44$, log-rank test)

Figure 2.

Kaplan-Meier curve depicting graft survival between transplants with a match at HLA-C locus versus those with no match. Number at risk for each cohort at 5, 10, 15 and 20 years post-transplant are shown below the curve. There was no difference in graft survival between HLA-DQ-no (median 13.1yrs, 95%CI 11.7–14.6yrs) versus HLA-DQ-match (median 13.0yrs, 95%CI 11.4–14.6, $p=0.80$, log-rank test)

Table 1

Comparison of transplants with no match at HLA-C locus versus transplants with a C-locus match.

	Transplants with complete C-locus typing (n=2429)	no C-locus match (n=1528)	C-locus match (n=901)	p-value
Recipient Age (years)	5 (0–13)	5 (0–13)	6 (0–13)	0.71
Transplant Year	2006 (1996–2010)	2005 (1996–2009)	2007 (1997–2010)	0.003
Serum Creatinine (mg/dL)	0.5 (0.4–0.8)	0.5 (0.4–0.8)	0.5 (0.4–0.7)	0.64
Total Bilirubin (mg/dL)	0.7 (0.4–1.2)	0.7 (0.4–1.3)	0.7 (0.4–1.2)	0.39
Ischemic Time (hours)	3.4 (2.7–4.2)	3.4 (2.7–4.2)	3.4 (2.7–4.1)	0.12
Donor-Recipient weight ratio	1.27 (1–1.7)	1.3 (1.0–1.7)	1.3 (1.0–1.6)	0.75
IV* Inotropes	1055 (43.4%)	653 (42.7%)	402 (44.6%)	0.37
Recipient on Ventilator	375 (15.2%)	222 (14.5%)	153 (17.0%)	0.11
Recipient on VAD	129 (5.7%)	89 (5.8%)	40 (4.4%)	0.13
Recipient on ECMO	95 (3.9%)	55 (3.6%)	40 (4.4%)	0.3
Positive or Indeterminate Crossmatch	162 (6.6%)	96 (6.2%)	66 (7.3%)	0.34
3 matches at A, B, and DR	153 (6.3%)	46 (3.0%)	107 (11.9%)	<0.01
<i>Cardiac Diagnosis</i>				
Cardiomyopathy	1195 (49.2%)	740 (48.4%)	455 (50.5%)	0.64
Congenital Heart Disease	995 (40.9%)	636 (41.6%)	359 (39.8%)	
Retransplant	140 (5.8%)	91 (6%)	49 (5.4%)	
Other	99 (4%)	61 (4%)	38 (4.2%)	

* IV=intravenous,

** VAD=ventricular assist device,

ECMO=extracorporeal membrane oxygenator

Table 2

Comparison of transplants with no match at HLA-DQ locus versus transplants with a DQ locus match.

	Transplants with complete DQ-locus typing (n=3498)	no HLA-DQ match (n=1837)	HLA-DQ match (n=1661)	p-value
Recipient Age (years)	6 (0–13)	6 (0–13)	6 (0–13)	0.31
Transplant Year	2004 (1997–2009)	2004 (1997–2009)	2004 (1995–2009)	0.78
Serum Creatinine (mg/dL)	0.5 (0.5–0.8)	0.5 (0.4–0.8)	0.5 (0.4–0.8)	0.45
Total Bilirubin (mg/dL)	0.7 (0.4–1.3)	0.7 (0.4–1.3)	0.7 (0.4–1.3)	0.7
Ischemic Time (hours)	3.5 (2.7–4.2)	3.5 (2.8–4.2)	3.4 (2.6–4.2)	0.06
Donor-Recipient weight ratio	1.3 (1–1.6)	1.3 (1.0–1.6)	1.3 (1.0–1.6)	0.4
IV* Inotropes	1494 (43.1%)	792 (43.1%)	702 (42.3%)	0.61
Recipient on Ventilator	539 (15.5%)	284 (15.5%)	255 (15.4%)	0.93
Recipient on VAD	178 (5.1%)	88 (5.1%)	90 (5.4%)	0.34
Recipient on ECMO	128 (3.7%)	68 (3.7%)	60 (3.6%)	0.89
Positive or Indeterminate Crossmatch	353 (7.2%)	140 (8.5%)	113 (7.5%)	0.27
3 matches at A, B and DR loci	142 (4.1%)	36 (3.2%)	106 (9.8%)	<0.01
<i>Cardiac Diagnosis</i>				
Cardiomyopathy	1750 (50%)	931 (51%)	819 (49%)	0.2
Congenital Heart Disease	1392 (39.9%)	730 (40%)	654 (39%)	
Retransplant	219 (6.3%)	103 (5.6%)	116 (7%)	
Other	137 (3.9%)	65 (3.5%)	72 (4.3%)	

* IV=intravenous,

** VAD=ventricular assist device,

ECMO=extracorporeal membrane oxygenator