HLA-DQ Mismatching and Kidney Transplant Outcomes

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Abstract

Background and objectives Recent evidence suggests that HLA epitope-mismatching at HLA-DQ loci is associated with the development of anti-DQ donor-specific antibodies and adverse graft outcomes. However, the clinical significance of broad antigen HLA-DQ mismatching for graft outcomes is not well examined.

Design, setting, participants, & measurements Using the United Network Organ Sharing/the Organ Procurement and Transplantation Network (UNOS/OPTN) data, patients with primary kidney transplants performed between 2005 and 2014 were included. Patients were classified as having either zero HLA-DQ mismatches, or one or two HLA-DQ mismatches. Primary outcomes were death-censored graft survival and incidence of acute rejection.

Results A total of 93,782 patients were included. Of these, 22,730 (24%) and 71,052 (76%) received zero and one or two HLA-DQ mismatched kidneys, respectively. After adjusting for variables including HLA-ABDR, HLA-DQ mismatching was associated with a higher risk of graft loss in living kidney donor recipients with an adjusted hazard ratio (HR) of 1.18 (95% confidence interval [95% CI], 1.07 to 1.30; $P<0.01$), but not in deceased kidney donor recipients (HR, 1.05; 95% CI, 0.98 to 1.12; $P=0.18$) (P value for interaction <0.01). When taking cold ischemic time into account, HLA-DQ mismatching was associated with a higher risk of graft loss in deceased kidney donor recipients with cold ischemic time ≤17 hours (HR, 1.12; 95% CI, 1.02 to 1.27; $P=0.002$), but not in deceased kidney donor recipients with cold ischemic time >17 hours (HR, 0.97; 95% CI, 0.88 to 1.06; $P=0.49$) (P value for interaction <0.01). Recipients with one or two HLA-DQ mismatched kidneys had a higher incidence of acute rejection at 1 year, with adjusted odds ratios of 1.13 (95% CI, 1.03 to 1.23; $P<0.01$) in deceased donor and 1.14 (95% CI, 1.03 to 1.27; $P=0.02$) in living donor kidney transplant recipients. Specific donor-DQ mismatches seemed to be associated with the risk of acute rejection and graft failure, whereas others did not.

Conclusions HLA-DQ mismatching is associated with lower graft survival independent of HLA-ABDR in living donor kidney transplants and deceased donor kidney transplants with cold ischemia time ≤17 hours, and a higher 1-year risk of acute rejection in living and deceased donor kidney transplants.

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Introduction

HLA matching provides benefits in improving outcomes in kidney transplantation (1–3) and remains part of the kidney allocation. HLA-DR matching has a much greater effect on graft outcomes compared with matching at the HLA-A or -B locus (4,5).

Although HLA-DQ does not factor into organ allocation, its relative importance has been increasingly recognized. Recipients with *de novo* anti-DQ donor-specific antibodies have a higher incidence of acute rejection, transplant glomerulopathy, and graft loss (6–9).

The effect of broad antigen HLA-DQ mismatching on kidney transplantation has not been clearly established. Although older studies found no significant correlation between HLA-DQ mismatching and graft outcomes (10–13), more recent data from the Australia and New Zealand Dialysis and Transplant Registry suggested that HLA-DQ mismatching affects outcomes (14).

Broad antigen HLA-DQ matching between each recipient and donor on the basis of serologic typing is available for the majority of kidney transplant recipients in the United Network for Organ Sharing (UNOS) registry (15). Using UNOS data, we sought to determine the effect of HLA-DQ matching on acute rejection and graft loss after kidney transplantation.

Materials and Methods

Data Source and Study Population

We used the UNOS database to select adult patients with ESKD who received their first kidney-only transplant between January 1, 2005, and December 3, 2014. The last follow-up date of this study was March 31, 2017. We excluded patients whose data on HLA-DQ matching were not available and those who had discrepant donor HLA-DQ typing between initial typing and retyping. Because HLA-DQ1 and HLA-DQ3 serotypes are no longer used in current HLA typing, recipients or donors with these serotypes were excluded (see Figure 1). The primary outcomes were analyzed using this cohort. The clinical and research activities being reported are consistent with the principles of the Declaration of Istanbul, as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

To examine the effect of each HLA-DQ antigen mismatches, we excluded recipients with HLA-DR mismatches and two HLA-DQ mismatches. We compared one HLA-DQ mismatches with zero HLA-DQ mismatches in a subgroup analysis. We counted an antigen mismatch in the host versus graft direction when the donor expressed a particular DQ antigen that the recipient did not. There were seven single donor HLA-DQ mismatched antigens identified (HLA-DQ2, -DQ4, -DQ5, -DQ6, -DQ7, -DQ8, and -DQ9). The subanalyses of the secondary outcomes were analyzed using the three cohorts depicted in Figure 2.

Outcome Measures

The primary outcomes of this study were death-censored graft survival and the cumulative incidence of acute rejection at 1 year after the kidney transplantation. The outcomes were stratified by HLA-DQ mismatches (zero HLA-DQ versus one or two HLA-DQ mismatches) and donor type (deceased versus living). For kidney graft survival analyses, patients were censored for patient death, or at the last follow-up visits reported to UNOS.

We performed subanalyses for acute rejection at 1 year post-transplantation, all-cause graft failure, and graft failure due to chronic allograft nephropathy at 10 years post-transplantation, for each single donor HLA-DQ mismatched antigen.

Statistical Analyses

Baseline characteristics were described using medians with interquartile ranges, or frequencies, where appropriate. To compare categorical and continuous variables between HLA-DQ matched and mismatched kidney transplant recipients, the chi-squared and Kruskal–Wallis tests were used. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of death-censored graft survival were calculated using Cox proportional hazard models. Acute rejection was examined using logistic regression. The covariates included were recipient-, donor-, and transplant-related characteristics as shown in Table 1. To assess for interactions between HLA-DQ mismatching and donor types on primary outcomes, an interaction term was created and entered in the multivariable model. To assess the effect of HLA-DQ mismatching on outcome measures in different cold ischemic time periods, interactions between HLA-DQ mismatching and cold ischemic time were tested and the cohort was further divided into subgroups on the basis of various cold ischemic time cutoff points (*e.g.*, 0–14 versus >14 hours; 0–17 versus >17 hours;

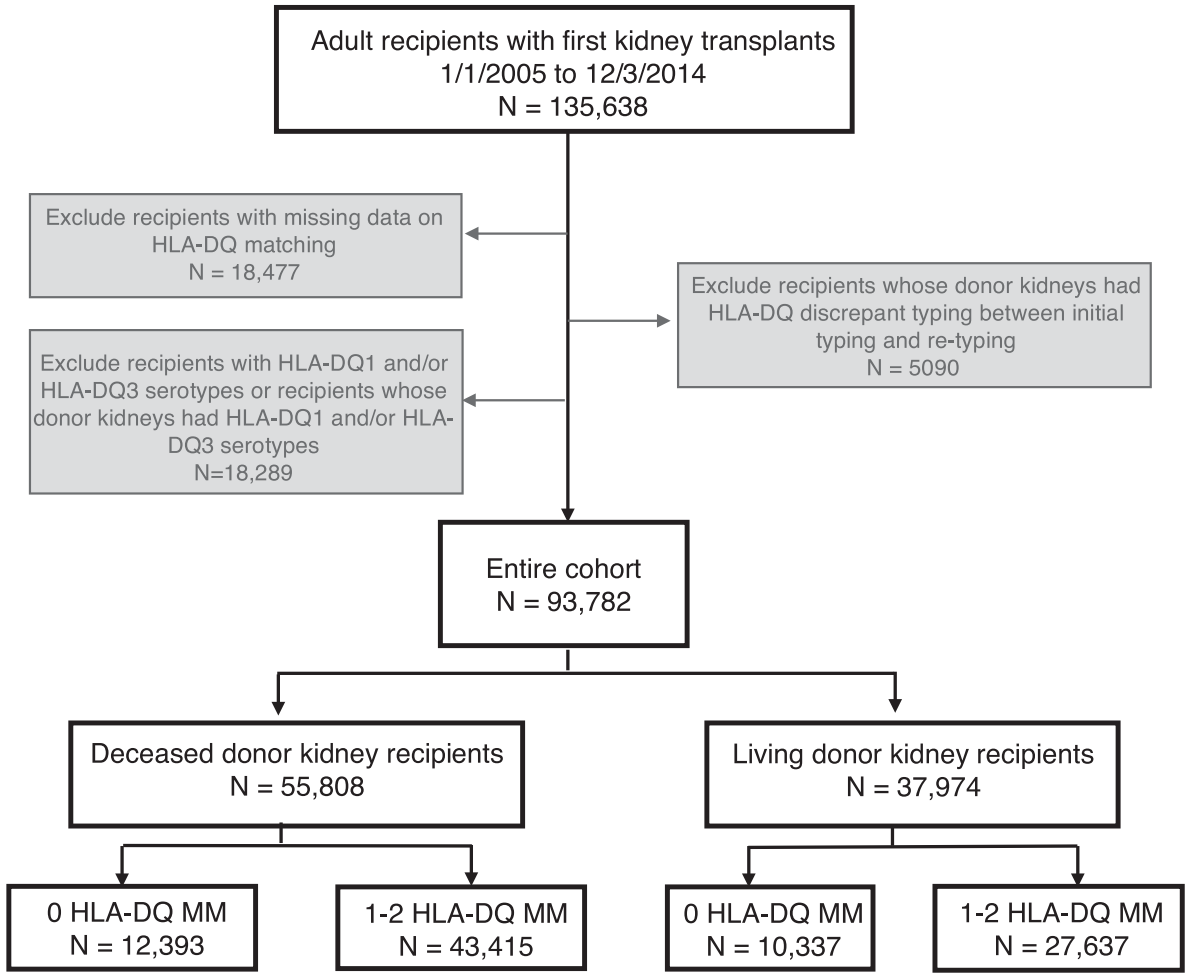

Figure 1. | Patients who had missing data on HLA-DQ matching, discrepant data between donor's initial HLA-DQ typing and retyping, and patients who had HLA-DQ1 and/or HLA-DQ3 serotypes or patients whose donor kidneys had HLA-DQ1 and/or HLA-DQ3 serotypes were excluded in the patient selection process for the primary outcome analyses. MM, mismatches.

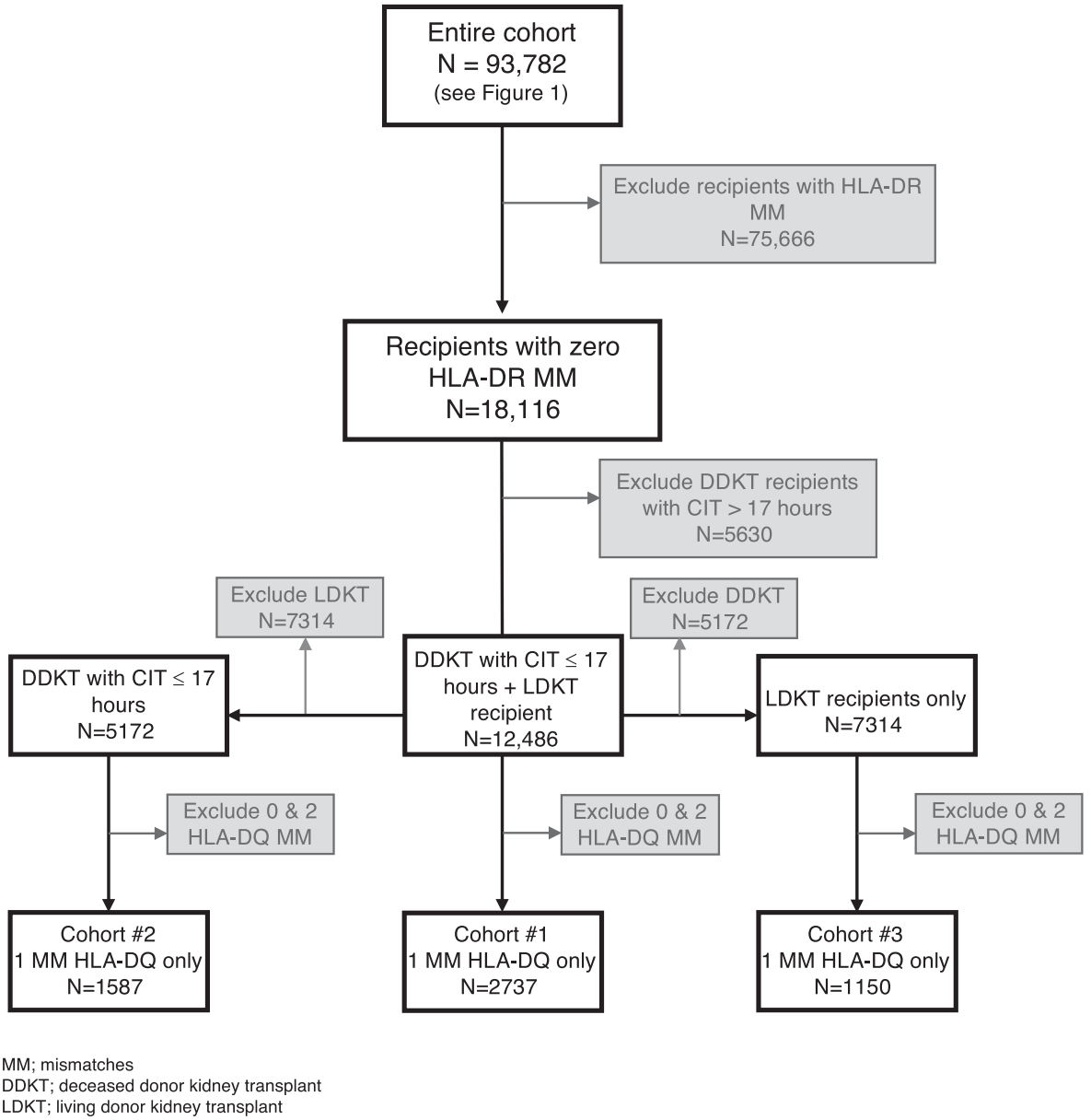

Figure 2. | Patients with HLA-DR mismatches and two HLA-DQ mismatches were excluded to better examine the effect of each HLA-DQ antigen mismatches. These recipients were divided into three cohorts: (*1*) deceased donor kidney transplant (DDKT) recipients with cold ischemic time of ≤17 hours and living donor kidney transplant (LDKT) recipients, (*2*) deceased donor kidney transplant recipients with cold ischemic time (CIT) of ≤17 hours only, and (*3*) living donor kidney transplant recipients only. MM, mismatches.

0–20 versus >20 hours). The Cox and logistic regression models were reapplied on these subgroups. Sensitivity analyses were conducted using different cohort restrictions and models for multivariable analysis. The chi-squared test was used for the analyses of the secondary outcomes. All *P* values were two-tailed, and *P* values of <0.05 were considered significant. Stata version 13 (StataCorp., College Station, TX) was used for all statistical analyses.

Results

Patients

Of 135,638 patients transplanted between 2005 and 2014, 18,477 (14%) were excluded from the analysis due to missing data on HLA-DQ matching, 5090 (4%) were excluded because of discrepancy between donor's initial HLA-DQ typing and retyping, and 18,289 (14%) were excluded because either recipient, donor, or both had HLA-DQ1 and/or HLA-DQ3 (see Figure 1). There were 93,782 patients in the final cohort, with a median follow-up time of 4.1 years (interquartile range, 2.8–6.6 years).

Baseline Characteristics

Baseline characteristics of the study population stratified by HLA-DQ mismatches (zero versus one or two HLA-DQ mismatches) and donor type (deceased versus living) are described in Table 1. Deceased kidney recipients who received zero HLA-DQ mismatched kidneys were more

Table 1. Baseline characteristics stratified by HLA-DQ mismatches and donor types

Characteristics	Deceased Donor Kidney Transplant		Living Donor Kidney Transplant	
	Zero HLA-DQ Mismatch (*n*=12,393)	One or Two HLA-DQ Mismatches (*n*=43,415)	Zero HLA-DQ Mismatch (*n*=9791)	One or Two HLA-DQ Mismatches (*n*=27,262)
Men, %	57	61	60	63
Age, median (25th, 75th)	55 (46, 63)	56 (45, 63)	49 (37, 59)	50 (39, 60)
Race, %				
White	51	40	64	66
Black	28	36	15	14
Hispanic	15	15	15	14
Other	6	9	6	6
Recipient BMI, median (25th, 75th)	28.0 (24.4, 32.0)	27.8 (24.3, 32.0)	27 (23.4, 31.2)	27.5 (23.9, 31.6)
Diabetes, %	37	37	27	30
Preemptive, %	13	9	35	34
Peak PRA, %				
Missing	19	22	22	20
≤10	53	58	63	67
11–30	7	7	6	6
>30	22	14	9	7
HLA-DR mismatch, %				
0	59	8	59	4
1	34	48	36	58
2	8	44	4	38
HLA-A mismatch, %				
0	34	9	41	14
1	29	39	47	54
2	36	52	12	32
HLA-B mismatch, %				
0	32	5	36	6
1	22	24	48	48
2	46	71	16	46
CMV serostatus, %				
D^+/R^-	19	18	14	16
D^+/R^+	43	46	36	34
D^-/R^+	24	24	23	23
D^-/R^-	13	12	13	12
Donor age, median (25th, 75th)	39 (24, 50)	42 (26, 53)	41 (32,50)	42 (33,51)
Male donors, %	60	60	41	38
Donor race, %				
White	72	68	66	70
Black	12	15	14	12
Hispanic	13	14	15	13
Other	3	4	6	5
Donor hypertension, %	25	30	3	3
ECD, % (only for deceased donor kidney transplant)	12	19	N/A	N/A
Cold ischemic time in hours, median (25th, 75th) (only for deceased donor kidney transplant)	17 (12, 22)	16 (11, 22)	N/A	N/A
KDPI percentile (25th, 75th) (only for deceased donor kidney transplant)	43 (22, 65)	51 (28, 73)	N/A	N/A
Transplant year, %				
2005–2008	30	26	36	32
2009–2011	32	34	33	34
2012–2014	38	40	31	34
Induction therapy, %				
Thymoglobulin	51	53	38	43
Alemtuzumab	14	13	14	16
Basiliximab	19	19	26	23
Other induction	5	4	7	6
No induction	15	14	17	14

Table 1. (Continued)

Characteristics	Deceased Donor Kidney Transplant		Living Donor Kidney Transplant	
	Zero HLA-DQ Mismatch (*n*=12,393)	One or Two HLA-DQ Mismatches (*n*=43,415)	Zero HLA-DQ Mismatch (*n*=9791)	One or Two HLA-DQ Mismatches (*n*=27,262)
Maintenance therapy, %				
Tacrolimus	90	90	86	88
Cyclosporine	5	4	7	6
Mycophenolic acid	94	94	91	92
Azathioprine	0.4	0.3	0.5	0.3
Sirolimus	2	2	4	4
Steroids	67	68	59	60
Delayed graft function	22	26	3	3

BMI, body mass index; PRA, panel reactive antibody; CMV, cytomegalovirus; D, donor; R, recipient; ECD, expanded criteria donors; N/A, not applicable; KDPI, Kidney Donor Profile Index.

likely to be white, have preemptive transplants, and lower Kidney Donor Profile Index scoring kidneys. Both deceased and living kidney donor recipients who had zero HLA-DQ mismatches were more likely to receive zero HLA-ABDR mismatched kidneys. Of those with zero HLA-DR mismatched kidneys, 33% and 16% were mismatched at the HLA-DQ locus in deceased and living kidney donor recipients, respectively. A greater proportion of deceased donor recipients with one or two HLA-DQ mismatches experienced delayed graft function (DGF) compared with recipients with zero HLA-DQ matched kidneys (26% versus 22%, respectively). A table comparing the characteristics of the patients excluded from the analyses with those that were included is provided in the Supplemental Material (Supplemental Table 1).

Death-Censored Graft Survival

Cox proportional hazard models were used to assess the effect of HLA-DQ mismatching on graft survival. There was a significant interaction between HLA-DQ mismatching and donor types on death-censored graft survival (P value for interaction <0.01). In univariable analyses, one or two HLA-DQ mismatched kidneys were associated with a significant greater risk of death-censored graft loss in both deceased and living cohorts (HR, 1.29; 95% CI, 1.22 to 1.36; $P<0.001$ in deceased donor cohort and HR, 1.35; 95% CI, 1.25 to 1.46; $P<0.001$ in living donor cohort) when compared with zero HLA-DQ mismatched kidneys. In multivariable analyses adjusted for HLA-ABDR and other potential risk factors (see Table 2), one or two HLA-DQ mismatched kidneys were associated with a significantly greater risk of graft loss in the living donor cohort (HR, 1.18; 95% CI, 1.07 to 1.30; $P<0.001$) when compared with zero HLA-DQ mismatched kidneys. HLA-DQ mismatches were not associated with graft failure in the deceased donor cohort.

Acute Rejection at 1-Year after Transplantation

The cumulative incidence of acute rejection in recipients who received zero HLA-DQ mismatched kidneys was significantly lower than one or two HLA-DQ mismatched kidneys (7% versus 11%; $P<0.001$). In the unadjusted logistic regression models, one or two HLA-DQ mismatched kidneys were associated with a significant greater risk of acute rejection with an unadjusted odds ratio (OR) of 1.41 (95% CI, 1.31 to 1.51; $P<0.001$) in the deceased donor cohort, and an unadjusted OR of 1.66 (95% CI, 1.53 to 1.81; $P<0.001$) in the living donor cohort. These differences persisted in the multivariable models after adjusting for HLA-ABDR, recipient, donor, transplant factors, and initial immunosuppression. HLA-DQ mismatches continued to have a significant effect on acute rejection in both deceased and living donor cohorts, with an adjusted OR of 1.13 (95% CI, 1.03 to 1.23; $P<0.01$) and 1.14 (95% CI, 1.03 to 1.27; $P=0.02$), respectively (Table 3).

The Effect of Cold Ischemic Time and HLA-DQ Mismatches on Outcomes

We further divided the deceased donor cohort according to cold ischemic time (short versus prolonged), using various cutoff points as there were significant interactions between HLA-DQ mismatching and cold ischemic time on primary outcomes when cold ischemic time was treated as an independent continuous variable ($P<0.01$ for death-censored graft survival and $P=0.01$ for acute rejection). Median cold ischemic time in the deceased donor cohort was 16.4 hours (interquartile range, 11.3–22.1 hours). Cold ischemic time of 17 hours appeared to be the optimal cutoff point as it yielded the highest HR and OR and the lowest P values for both primary outcomes. A total of 21% of recipients with cold ischemic time of ≤17 hours had DGF, whereas 29% of recipients with cold ischemic time >17 hours had DGF. HLA-DQ mismatching was an independent risk factor for a higher risk of graft loss and acute rejection when cold ischemic time was ≤17 hours, with an HR for graft loss of 1.12 (95% CI, 1.02 to 1.27; $P=0.02$) and OR for acute rejection of 1.20 (95% CI, 1.06 to 1.35; $P=0.003$), as shown in Table 4. Interestingly, HLA-DQ mismatching did not have an effect on death-censored graft survival and acute rejection when cold ischemic time was >17 hours.

Sensitivity Analyses

A sensitivity analysis was conducted to examine the association between HLA-DQ mismatching and primary

Table 2. Cox proportional hazards models for death-censored graft survival (DCGS) between recipients with HLA-DQ matched versus HLA-DQ mismatched kidneys

		Unadjusted		Adjusted Model[a]	
DCGS	Incidence	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Deceased					
0 DQ MM	1465/12,347	Reference		Reference	
1 or 2 DQ MM	6189/43,208	1.29 (1.22 to 1.36)	<0.001	1.05 (0.98 to 1.12)	0.18
Living					
0 DQ MM	841/10,321	Reference		Reference	
1 or 2 DQ MM	2876/27,612	1.35 (1.25 to 1.46)	<0.001	1.18 (1.07 to 1.30)	<0.001

MM, mismatches; 95% CI, 95% confidence interval.
[a]Adjusted for HLA-DR, HLA-A, and HLA-B mismatches, race/ethnicity, sex, body mass index, preemptive, panel reactive antibody, diabetes, donor age, race/ethnicity, sex, donor hypertension, cytomegalovirus serostatus, immunosuppression, transplant periods, and expanded donor criteria status (for deceased donor kidney transplants).

outcomes in various cohort restrictions and several levels of multivariable analysis. The significant association between HLA-DQ matching status and primary outcomes were maintained in living and deceased kidney donor recipients with cold ischemic time of ≤17 hours. There was no association between HLA-DQ mismatching and primary outcomes in deceased kidney donor recipients with cold ischemic time >17 hours, even after excluding those with zero HLA-ABDR mismatches, ensuring that these findings were not confounded by the effect of zero HLA-ABDR organ sharing (Supplemental Table 2, A and B).

The Effect of the Incremental Number of HLA-DQ Mismatching and Outcomes

We assessed a linear association between an incremental number of HLA-DQ mismatching and primary outcomes by having three levels of exposure: zero, one, and two HLA-DQ mismatches in patients who received a kidney from living and deceased donors with cold ischemic time of 17 hours≤. When compared with zero HLA-DQ mismatches, one and two HLA-DQ mismatches had a higher risk of acute rejection in an incremental fashion, with an OR of 1.22 (95% CI, 1.12 to 1.22; $P<0.001$) in one HLA-DQ mismatches and 1.32 (95% CI, 1.20 to 1.44; $P<0.001$) in two HLA-DQ mismatches. Two HLA-DQ mismatched kidneys were associated with a higher risk of acute rejection when compared with one HLA-DQ mismatched kidneys, with an OR of 1.10 (95% CI, 1.03 to 1.17; $P=0.004$). There was no linear association between an incremental number of HLA-DQ mismatching and death-censored graft survival (Supplemental Table 3, A and B).

Interaction between HLA-DQ and HLA-DR Mismatches

There was a significant interaction between HLA-DQ and HLA-DR on acute rejection (*P* value for interaction =0.01). In the analyses stratified by HLA-DR mismatches, the association between HLA-DQ and acute rejection was more pronounced in recipients who received zero HLA-DR mismatches, with an adjusted OR of 1.35 (95% CI, 1.14 to 1.60; $P=0.001$). There was also an association between HLA-DQ and acute rejection in recipients who received one or two HLA-DR mismatches, but to a lesser extent, with an adjusted OR of 1.16 (95% CI, 1.07 to 1.27; $P=0.001$). There was no interaction between HLA-DQ and HLA-DR on death-censored graft survival (*P* value for interaction =0.10; Supplemental Table 4).

The Effect of HLA-DQ Antigen Mismatch in the Host versus Graft Direction

To better understand the role of each HLA-DQ antigen mismatch on acute rejection and graft loss rate, we

Table 3. Logistic regression models for cumulative incidence of acute rejection at 1 year after transplantation between recipients with HLA-DQ matched versus HLA-DQ mismatched kidneys

		Unadjusted		Adjusted Model[a]	
Acute Rejection	Incidence	Odd Ratio (95% CI)	*P* Value	Odd Ratio (95% CI)	*P* Value
Deceased					
0 DQ MM	950/12,393	Reference		Reference	
1 or 2 DQ MM	4540/43,415	1.41 (1.31 to 1.51)	<0.001	1.13 (1.03 to 1.23)	<0.01
Living					
0 DQ MM	694/10,337	Reference		Reference	
1 or 2 DQ MM	2957/27,637	1.66 (1.53 to 1.81)	<0.001	1.14 (1.03 to 1.27)	0.02

MM, mismatches; 95% CI, 95% confidence interval.
[a]Adjusted for HLA-DR, HLA-A, and HLA-B mismatches, race/ethnicity, sex, body mass index, preemptive, panel reactive antibody, diabetes, donor age, race/ethnicity, sex, donor hypertension, cytomegalovirus serostatus, immunosuppression, transplant periods, and expanded donor criteria status (for deceased donor kidney transplants).

Table 4. Cox proportional hazards model for death-censored graft survival (DCGS) and logistic regression model for cumulative incidence of acute rejection at 1 year after transplantation in deceased donor kidney transplantation between recipients with HLA-DQ matched versus HLA-DQ mismatched kidneys, stratified by cold ischemic times

Model	Incidence	Cold ischemic time 0–17 h		Cold ischemic time >17 h	
		HR[a] (95% CI)	*P* Value	HR[a] (95% CI)	*P* Value
DCGS, deceased donor					
0 DQ MM	681/6215	Reference		Reference	
1 or 2 DQ MM	3128/23,037	1.12 (1.02 to 1.27) Odds Ratio[a]	0.02	0.97 (0.88 to 1.06) Odds Ratio[a]	0.49
Acute rejection, deceased donor					
0 DQ MM	467/6227	Reference		Reference	
1 or 2 DQ MM	2393/23,127	1.20 (1.06 to 1.35)	0.003	1.05 (0.92 to 1.19)	0.46

MM, mismatches; 95% CI, 95% confidence interval.
[a]Adjusted for HLA-DR, HLA-A, and HLA-B mismatches, race/ethnicity, sex, body mass index, preemptive, panel reactive antibody, diabetes, donor age, race/ethnicity, sex, donor hypertension, cytomegalovirus serostatus, immunosuppression, transplant periods, and expanded donor criteria status (for deceased donor kidney transplants).

excluded all of the patients who had any HLA-DR mismatch. Deceased kidney donor recipients with cold ischemic time >17 hours were also excluded. We analyzed the subset of patients who received an allograft with only one DQ mismatch.

The acute rejection rate of patients receiving one HLA-DQ mismatched kidneys was significantly higher compared with patients with zero HLA-DQ mismatch (8% versus 5%; $P<0.001$), as shown in Table 5. Notably, when we further stratified donor mismatching by HLA-DQ antigen, we found that certain donor HLA-DQ antigen mismatches were associated with higher rate of acute rejection. Donor DQ8 antigen mismatching was significantly associated with a higher rate of acute rejection in both deceased and living donor grafts.

The rate of graft failure from any cause at 10 years was higher in recipients with one HLA-DQ compared with zero HLA-DQ mismatched kidneys in all three cohorts (Table 5). When we stratified donor mismatching by HLA-DQ antigen, certain donor HLA-DQ antigen mismatching seemed to be responsible for the higher rate of graft loss due to any cause, especially DQ5 mismatching. DQ5 mismatching association with graft loss was statistically significant in living donor kidney recipients. The rate of graft loss was numerically higher in deceased kidney donor recipients with DQ5 mismatching, although the difference was not significant. Graft loss due to chronic allograft nephropathy was not significantly associated with one HLA-DQ mismatches compared with zero HLA-DQ mismatches. However, DQ5 mismatching was associated with graft loss due to chronic allograft nephropathy in deceased kidney donor recipients (Table 5).

Discussion

This analysis of 93,782 kidney-only transplants in the United States over 10 years is the largest retrospective study to date to evaluate the effects of HLA-DQ mismatching on transplant outcomes in the era of modern HLA typing. We demonstrated that HLA-DQ mismatched kidneys have a higher risk of acute rejection when compared with HLA-DQ matched kidneys. HLA-DQ mismatching influences graft survival in living kidney donor recipients and in deceased kidney donor recipients with cold ischemic time ≤17 hours.

Because DQ loci are in close genetic linkage to HLA-DR, the effects of HLA-DQ matching have been understated in the past (11,16). We observed a considerable amount of discordance between HLA-DQ and HLA-DR mismatches, as 41% of recipients of HLA-DQ matched kidneys had HLA-DR mismatches and 26% of recipients of HLA-DR matched kidneys had HLA-DQ mismatches. These findings are consistent with a study by Lim *et al.* (14).

There is evidence that anti-DQ donor-specific antibodies are the predominant *de novo* donor-specific antibodies after transplantation and have a detrimental effect on outcomes (6–9,17). HLA epitope-mismatching at HLA-DQ loci has been shown to be associated with the development of anti-DQ donor-specific antibodies and transplant glomerulopathy (18,19). Wiebe *et al.* found that an HLA-DQ epitope-mismatched threshold of ≥17 was significantly associated with *de novo* anti-DQ donor-specific antibodies. After a median follow-up of 6.9 years, only 2.7% of recipients with <17 HLA-DQ epitope-mismatches developed *de novo* anti-DQ donor-specific antibodies (18). Sapir-Pichhadze *et al.* conducted a nested case-control study on 52 kidney transplant recipients with transplant glomerulopathy. In this study, an increasing number of HLA-DR and HLA-DQ epitope-mismatches were associated with the development of transplant glomerulopathy (19). All these findings suggest that we could potentially minimize immunogenic risks by avoiding HLA-DQ mismatches, thereby improving outcomes. However, identification of HLA epitope-mismatching is not routinely performed in most centers.

The effect of broad antigen HLA-DQ mismatching on kidney allograft outcomes has not been clearly established. Freedman *et al.* (13) concluded that HLA-DQ mismatching does not have a significant effect on graft survival. Similarly, Sasaki and Idica (12) showed that HLA-DQ does not have an effect on graft survival. However, these studies were conducted when the HLA-DQ typing technique was less advanced and precise compared with the current era. More recently, Lim *et al.* (14) found that HLA-DQ mismatching is associated with a higher risk of acute rejection

Table 5. The rate of acute rejection at 1 year, the rate of graft loss due to all causes, and the rate of graft loss due to CAN at 10 years in three different cohorts

Cohort	DDKT with CIT ≤17 h and LDKT					DDKT with CIT ≤17 h Only					LDKT Only				
	AR (at 1 yr)	*P* Value	Overall Graft Loss (at 10 yr)	*P* Value	Graft Loss due to CAN (at 10 yr)	AR (at 1 yr)	*P* Value	Overall Graft Loss (at 10 yr)	*P* Value	Graft Loss due to CAN (at 10 yr)	AR (at 1 yr)	*P* Value	Overall Graft Loss (at 10 yr)	*P* Value	Graft Loss due to CAN (at 10 yr)	*P* Value
Zero DQ mismatch	5.4 (515/9553)		8.0 (769/9553)		2.0 (195/9553)	6.3 (218/3436)		9.4 (322/3436)		2.4 (83/3436)	4.9 (297/6117)		7.3 (447/6117)		1.8 (112/6117)	
Overall one DQ mismatch	8.0 (219/2737)	<0.001[a]	11.1 (305/2737)	<0.001[a]	1.9 (70/2737)	8.0 (126/1587)	0.04[a]	12.4 (197/1587)	0.001[a]	2.7 (43/1587)	8.1 (93/1150)	<0.001[a]	9.4 (108/1150)	0.02[a]	2.4 (27/1150)	0.24
Single donor DQ mismatch																
DQ2	6.5 (18/278)	0.32	9.4 (26/278)	0.32	0.7 (2/278)	6.2 (10/161)	0.39	9.9 (16/161)	0.32	1.2 (2/161)	6.8 (8/117)	0.60	8.6 (10/117)	0.74	0 (0/117)	0.08
DQ4	4.7 (6/129)	0.15	11.6 (15/129)	0.86	1.6 (2/129)	5.3 (4/75)	0.39	13.3 (10/75)	0.80	0 (0/75)	3.7 (2/54)	0.23	9.3 (5/54)	0.97	3.7 (2/54)	0.50
DQ5	4.4 (8/181)	0.07	17.7 (32/181)	0.004[b]	5.5 (10/181)	5.1 (5/98)	0.28	16.3 (16/98)	0.23	9.2 (9/98)	3.6 (3/83)	0.12	19.3 (16/83)	0.001[b]	1.2 (1/83)	0.48
DQ6	7.4 (28/379)	0.64	12.7 (48/379)	0.31	2.4 (9/379)	5.5 (12/217)	0.16	13.4 (29/217)	0.65	2.3 (5/217)	9.9 (16/162)	0.37	11.7 (19/162)	0.27	2.5 (4/162)	0.91
DQ7	8.5 (80/943)	0.50	10.0 (94/943)	0.16	3.2 (30/943)	9.1 (51/558)	0.19	11.7 (65/558)	0.50	3.4 (19/558)	7.5 (29/385)	0.63	7.5 (29/385)	0.13	2.9 (11/385)	0.42
DQ8	11.4 (60/526)	0.001[b]	10.7 (56/526)	0.69	2.1 (11/526)	11.1 (32/289)	0.03[b]	13.2 (38/289)	0.68	2.1 (6/289)	11.8 (28/237)	0.03[b]	7.6 (18/227)	0.29	2.1 (5/237)	0.79
DQ9	6.3 (19/300)	0.26	11.3 (34/300)	0.91	2.0 (6/300)	6.4 (12/188)	0.40	12.2 (23/188)	0.94	1.1 (2/188)	6.3 (7/112)	0.45	9.8 (11/112)	0.87	3.6 (4/112)	0.37

CAN, chronic allograft nephropathy; DDKT, deceased donor kidney transplant; CIT, cold ischemia time; LDKT, living donor kidney transplant; AR, acute rejection; MM, mismatches.
[a]Rate of acute rejection or graft failure was higher than zero DQ-MM with statistically significant difference ($P<0.05$).
[b]Rate of acute rejection or graft failure was higher than overall one DQ-MM with statistically significant difference ($P<0.05$).

independent of HLA-ABDR mismatches and initial immunosuppression. Our findings broaden the analysis to a larger United States cohort and confirm Lim *et al.*'s data. Unlike our study, Lim *et al.* did not find an effect of HLA-DQ mismatching on graft survival. The lack of association between HLA-DQ mismatching and graft loss in their study may be because of a relatively short follow-up time and fewer patients. Also, 87% of their patients were excluded because of missing data on HLA-DQ. Our study includes more patients and demonstrates an association between HLA-DQ mismatching and risk of acute rejection and graft loss.

Prolonged cold ischemic time is a strong risk factor for developing DGF and poorer graft outcomes (20,21). Lee *et al.* (22) described no graft survival advantages of zero HLA-ABDR mismatches if cold ischemic time was >36 hours, suggesting that the improved outcome as a result of better HLA matching can be offset by prolonged cold ischemic time. We confirm that HLA-DQ mismatching is significantly associated with acute rejection and graft loss. However, when zero HLA-DQ mismatched kidneys had >17 hours of cold ischemic time, the graft survival advantage was lost. Our analysis on the effect of cold ischemic time and HLA DQ mismatching on graft outcomes implies that avoiding HLA DQ mismatching may be less important than avoiding a long cold ischemic time to improve graft outcomes.

Furthermore, regardless of recipient DQ, when the kidney donor mismatch was DQ8, we found a higher risk of acute rejection. There were some donor HLA-DQ mismatches that did not impart a greater rate of acute rejection, such as HLA-DQ4. This suggests that the concept of worse and permissive/tolerable HLA mismatches may also be applicable to kidney transplantation as it is in hematopoietic stem cell transplant (23,24). Thus, a more refined approach to DQ mismatching may be important in improving short- and long-term outcomes. There was also a higher risk of graft loss in living kidney donor recipients when DQ5 was the donor mismatch. This information may be used in living donor selection.

We recommend increased vigilance for rejection when there are DQ mismatches, especially those that are less tolerable. Increased immunosuppression and/or more frequent post-transplant monitoring for donor-specific antibodies may be appropriate in these situations.

There are several limitations to our study, inherent to the retrospective design and use of registry data. There may be a potential for residual confounding from factors that are not captured in the database, particularly the lack of data on pretransplant and *de novo* donor-specific antibodies. Moreover, UNOS/OPTN registry does not specify the type of rejection (cellular versus humoral), which would have allowed us to better understand the correlation between HLA-DQ mismatching and acute rejection. Although the cause of graft loss is collected in the UNOS registry, 30% of recipients who experienced graft loss had the cause of graft loss coded as "other-specified." A total of 25% of patients had "chronic allograft nephropathy" as the cause of graft loss, which is a nonspecific term and does not differentiate among common causes. Thus, we were not able to investigate the association between DQ mismatching and chronic rejection. We assumed that the

diagnosis of chronic allograft nephropathy included the majority of chronic rejection diagnoses, and for this reason, we analyzed graft loss due to chronic allograft nephropathy.

In conclusion, our study identifies HLA-DQ mismatching as an independent risk factor for acute rejection and kidney allograft loss in the UNOS database. Our data show that when cold ischemic time exceeds 17 hours, the benefit conferred by improved HLA matching is obviated. Some specific donor DQ mismatches also appear to increase the risk of acute rejection and graft failure. A better understanding of the immunogenicity and antigenicity of each HLA-DQ mismatch combination in both broad antigen and epitope levels is required to identify high-risk recipients with highly immunogenic HLA-DQ mismatches, and guide personalized therapeutic and preventive strategies.

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Disclosures

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