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Rethinking the advantage of zero-HLA mismatches in unrelated living donor kidney transplantation: implications on kidney paired donation

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Summary

The OPTN/UNOS Kidney Paired Donation (KPD) Pilot Program allocates priority to zero-HLA mismatches. However, in unrelated living donor kidney transplants (LDKT)—the same donor source in KPD—no study has shown whether zero-HLA mismatches provide any advantage over >0 HLA mismatches. We hypothesize that zero-HLA mismatches among unrelated LDKT do not benefit graft survival. This retrospective SRTR database study analyzed LDKT recipients from 1987 to 2012. Among unrelated LDKT, subjects with zero-HLA mismatches were compared to a 1:1–5 matched (by donor age ±1 year and year of transplantation) control cohort with >0 HLA mismatches. The primary endpoint was death-censored graft survival. Among 32,654 unrelated LDKT recipients, 83 had zero-HLA mismatches and were matched to 407 controls with >0 HLA mismatches. Kaplan–Meier analyses for death-censored graft and patient survival showed no difference between study and control cohorts. In multivariate marginal Cox models, zero-HLA mismatches saw no benefit with death-censored graft survival (HR = 1.46, 95% CI 0.78–2.73) or patient survival (HR = 1.43, 95% CI 0.68–3.01). Our data suggest that in unrelated LDKT, zero-HLA mismatches may not offer any survival advantage. Therefore, particular study of zero-HLA mismatching is needed to validate its place in the OPTN/UNOS KPD Pilot Program allocation algorithm.

Introduction

The benefits of kidney transplantation over chronic dialysis with regard to patient survival are well known [1–3]. However, the gap between the available organ supply and the number of patients in need of a transplant keeps widening and waiting times for deceased donor kidney transplants keep increasing [4]. Living donor kidney transplants provide several advantages over deceased donor transplants such as shorter waiting time to transplant and superior graft and patient survival, but approximately one-third of potential living kidney donors are incompatible with their potential recipients [4–6]. Fortunately, kidney paired donation (KPD) has emerged as a promising solution which matches incompatible donor-recipient pairs who can exchange living donors and then proceed to transplantation.

Since the first KPD transplant in the United States in 2000, KPD has become the fastest growing source of transplantable kidneys [7]. In fact in 2011, KPD accounted for 7.4% of all living donor kidney transplants performed in the United States [8]. Despite this growth, many believe that we have yet to realize KPD's large-scale potential [9–11]. To reach its full potential and maximize an incompatible pair's matching opportunity, a KPD program needs to draw on the largest pool of donor–recipient pairs [6,7,10,12,13]. Therefore in 2010, the Organ Procurement and Transplantation Network (OPTN)/United Network for

Organ Sharing (UNOS) implemented the Kidney Paired Donation Pilot Program to be a nationwide system for the United States. As of February 2014, over 130 transplant centers in the United States participate in this program which accounts for over half of all eligible transplant centers [14].

It is well established that in *deceased* donor kidney transplants, zero-HLA mismatches among the traditional 6 major histocompatibility antigens at HLA-A, HLA-B, and HLA-DR offer a significant graft survival benefit over transplants with one or more HLA mismatches [15–22]. In addition, it has been reported that zero-HLA mismatched *living* donor kidney transplants appear to benefit graft survival as well [23–28]. Therefore, the OPTN/UNOS Kidney Paired Donation Pilot Program adopted the same definition of zero-HLA mismatching among the traditional 6 major histocompatibility antigens to award KPD allocation priority [29]. However, no study has shown whether zero-HLA mismatching actually provides a significant survival benefit in *unrelated* living donor kidney transplants like the ones used in KPD. We hypothesize that zero-HLA mismatches among *unrelated* living donor kidney transplants do not provide a significant benefit to graft survival over nonzero-HLA living donor grafts.

Materials and methods

Study population

Recipients with a living donor kidney-only transplant between the dates of October 1, 1987 to September 4, 2012 were identified using data from the Scientific Registry of Transplant Recipients (SRTR), which includes data on all donor, wait-listed candidates, and transplant recipients in the United States, collected by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services oversees the activities of the OPTN and SRTR contractors.

An unrelated living donor transplant recipient was identified by having a "nonbiological" living donor transplant in the donor relationship type field or being designated "unrelated" in the haplotype match field. The study group was defined as the unrelated living donor transplant recipients with zero-HLA mismatches at the traditional 6 antigens at HLA-A, HLA-B, and HLA-DR. Other nontraditional histocompatibility antigens were not considered for this study as they are not well reported in the SRTR and play no role in the zero-HLA mismatch allocation priority in the OPTN/UNOS Kidney Paired Donation Pilot Program. The controls were selected from the unrelated living donor recipients with >0 HLA mismatches at the previously defined 6 antigens and matched with the study group by donor age and year of transplant.

Matching procedure

A retrospective matched cohort was performed with matching ratio 1:1–5 (whichever is feasible) for study and control recipients. The purpose of matched cohort studies is to achieve reliable risk estimates of graft loss or mortality through precisely adjusting for confounding covariate. Donor age and year of transplant have been identified as important confounders for the association of HLA mismatch status and transplant survival [30]. Therefore, the study group was matched with the control group according to the similar donor age ($\pm$1 year) and identical year of transplant. To avoid unmatched study recipients and increase the power of the analysis, matching was carried out using a ratio of 1:1–5 where one study recipient was matched to 1–5 controls.

Outcome

The primary endpoints studied were time to events, including death-censored graft survival and patient mortality. Mortality data in the SRTR were augmented by linking with the Social Security Death Master File. Graft survival was defined by linking the SRTR data with the data from the Centers for Medicare & Medicaid Services. Death-censored graft survival was defined as the length of time from the transplant surgery to the first time graft loss after censoring all deaths that occurred prior to graft loss.

Covariates

Other covariates adjusted in the multivariate analysis included as follows: recipient age at time of transplant, recipient race and gender, final peak panel reactive antibody (PRA) prior to transplant, biopsy confirmed acute rejection, induction immunosuppression used, diabetes as primary cause of end stage renal disease (ESRD), and dialysis prior to transplant.

Statistical analysis

Baseline characteristics of the study and control groups were compared using the chi-square or Fisher's exact test for categorical variables, or the Student's *t*-test for continuous variables. Kaplan–Meier curves were utilized to delineate the survival distributions for the study and control groups, and a nonparametric log-rank statistic was performed to compare the hazards of the two groups. The multivariate survival analysis was conducted using a marginal Cox model for clustered time to event data, in which each matched set was indicated by a cluster and a robust covariance estimate [31] was implemented to account for the correlation within the matched pairs. All statistical

analyses were conducted with SAS 9.3 (Cary, NC). Statistical significance level was defined as $p < 0.05$. The study protocol was approved by the University of Florida Institutional Review Board (ID# IRB201400175) and conducted in accordance with the Declaration of Helsinki 2008 and the Declaration of Instanbul 2008.

Results

A total of 109,987 living donor kidney transplants were performed of which 32,654 (30%) were unrelated, 75,848 (69%) were related, and 1,485 (1%) where the relationship status was unknown. Among unrelated living donor kidney transplant recipients, we found 83 with zero-HLA mismatches, 31,986 with >0 HLA mismatches, and 585 with no HLA data available. Study subjects who received a zero-HLA mismatched unrelated living donor transplant ($N = 83$) were well distributed across 54 United States transplant centers and the matched controls ($N = 407$) were distributed across 142 United States transplant centers. Baseline characteristics between the study group and the matched control group were generally similar save for there were more female recipients in the study group than the control group (Table 1). In the matched control group, the median number of HLA mismatches was 5 [25% and 75%, Interquartiles: 5, 6].

Kaplan–Meier analysis for death-censored graft survival and patient survival among unrelated living donor transplants showed no difference between the zero-HLA mismatched (study) and >0 HLA mismatched (control) groups (Figures 1 and 2). In the zero-HLA mismatched group, the maximum duration of follow-up was 12.9 years which was largely driven by the majority (86%) of transplantations occurring on or after the year 1999. For the matched cohorts multivariate marginal Cox models, we found that zero-HLA mismatching was not associated with better death-censored graft survival (HR = 1.46, 95% CI 0.78–2.73, $P = 0.24$), but biopsy proven acute rejection was associated with worse graft survival (HR = 2.42, 95% CI 1.34–4.37, $P < 0.01$) as seen in Table 2. Also, patient survival does not appear to be enhanced from zero-HLA mismatching (HR = 1.43, 95% CI 0.68–3.01, $P = 0.35$). However, older recipient age was associated with poorer patient survival while the use of a lymphocyte depleting

Table 1. Baseline characteristics of the study and matched control cohorts.

Characteristic	Study cohort (0 HLA mismatch) ($N = 83$)	Control cohort (>0 HLA mismatch) ($N = 407$)	*P* value
Recipient age at time of transplant, Mean ± SD	45.1 ± 12.6	45.8 ± 12.3	0.6540
Black recipient, *N* (%)	7 (8.4)	43 (10.6)	0.5588
Female recipient, *N* (%)	40 (48.2)	143 (35.1)	0.0250
Previous kidney transplant recipient, *N* (%)	9 (10.8)	42 (10.3)	0.8867
Pediatric recipient, *N* (%)	1 (1.2)	5 (1.2)	>0.999
Diabetes as primary ESRD cause, *N* (%)	17 (20.5)	81 (19.9)	0.9041
Dialysis duration			
No prior dialysis, *N* (%)	25 (30.5)	128 (31.7)	0.8765
Dialysis <2 years, *N* (%)	40 (48.8)	202 (50.0)	
Dialysis ≥2 years, *N* (%)	17 (20.7)	74 (18.3)	
BMI			
Missing, *N* (%)	13 (15.7)	48 (11.8)	0.2868
Normal, *N* (%)	54 (65.1)	250 (61.4)	
Obese, *N* (%)	16 (19.3)	109 (26.8)	
Final peak PRA			
Missing, *N* (%)	2 (2.4)	8 (2.0)	0.5924
PRA <80, *N* (%)	76 (91.6)	384 (94.4)	
PRA ≥80, *N* (%)	5 (6.0)	15 (3.7)	
Induction with a lymphocyte depleting agent, *N* (%)	28 (33.7)	182 (44.7)	0.0654
Biopsy proven acute rejection, *N* (%)	4 (4.8)	35 (8.6)	0.3715
Donor age, mean ± SD	41.1 ± 10.6	41.2 ± 10.2	0.9574
Female donor, *N* (%)	55 (66.3)	242 (59.5)	0.2475
Black donor, *N* (%)	7 (8.4)	31 (7.6)	0.7998
Initial maintenance immunosuppression			
Tacrolimus, *N* (%)	59 (71.1)	268 (65.9)	0.3561
Cyclosporine, *N* (%)	19 (22.9)	122 (30.0)	0.1939
Mycophenolic acid, *N* (%)	59 (71.1)	315 (77.4)	0.2177
Corticosteroids, *N* (%)	57 (68.7)	306 (75.2)	0.2174

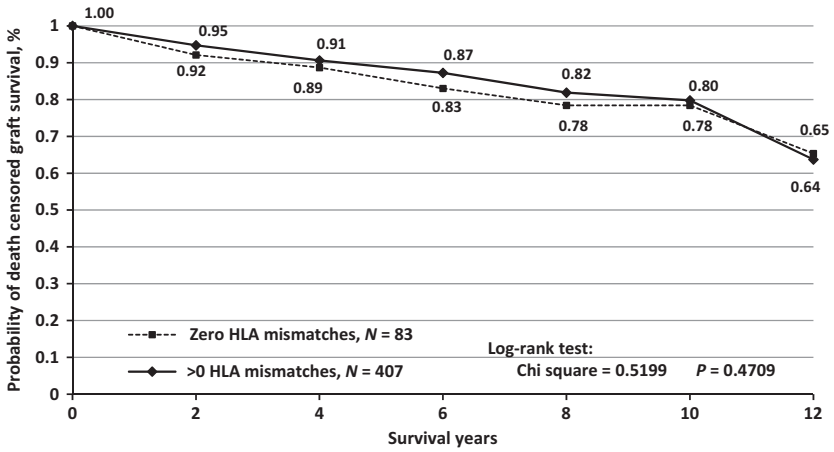

Figure 1 Matched cohorts Kaplan–Meier curves for death-censored graft survival in unrelated living donor kidney transplants, zero-HLA mismatches versus >0 HLA mismatches.

Table 2. Matched cohorts Marginal Cox Model for death-censored graft survival in unrelated living donor kidney transplants.

Parameter	*P* value	Hazard ratio	95% Confidence interval	
Zero-HLA mismatches v. >0 HLA mismatches	0.2403	1.456	0.778	2.725
Recipient age at time of transplant	0.1870	0.984	0.961	1.008
Black recipient	0.1887	1.637	0.785	3.411
Female recipient	0.3463	0.775	0.457	1.317
Final peak PRA ≥80 v. <80	0.7130	0.655	0.069	6.228
Biopsy proven acute rejection	0.0033	2.421	1.342	4.365
Induction with a lymphocyte depleting agent	0.4729	1.237	0.692	2.214
DM as primary cause of ESRD	0.4761	0.751	0.341	1.653
Dialysis <2 years versus no dialysis	0.3674	1.333	0.713	2.490
Dialysis ≥2 years versus no dialysis	0.1859	1.700	0.774	3.730

agent as induction immunosuppression was associated with improved patient survival (Table 3). Despite the baseline difference in recipient gender between the study and matched control groups, recipient gender was not associated with any significant difference in either death-censored graft survival or patient survival in our multivariate models.

To assess for consistency with prior literature, we performed a Kaplan–Meier analysis on all living donor kidney recipients and—similar to past reports—better death-censored graft survival was associated with zero-HLA mismatching when a cohort of related and unrelated living donor kidney recipients was combined (Figure 3). However, when those 2 groups were further subdivided into related and unrelated donor transplants, the associated graft survival benefit with zero-HLA mismatches disappeared in *unrelated* living donor transplants, but was retained in *related* living donor transplants (Figures 4 and 5). Also among all zero-HLA mismatched living donor transplants, a significant benefit in death-censored graft survival was seen in *related* over *unrelated* living donor transplants (Figure S1).

Discussion

The findings in this study come in the context of a fledgling national KPD program in the United States. We chose to analyze a cohort of *unrelated* living donor kidney transplant recipients because most potential KPD transplant recipients would have exhausted all related living donor options prior to KPD enrollment. Our data suggest that neither graft survival nor patient survival benefits from zero-HLA mismatching for the 6 classic antigens on HLA-A, HLA-B, and HLA-DR in kidney transplants from unrelated living donors. At first, this curious finding seems to conflict with prior literature, but when past reports analyzed zero-HLA mismatching in living donor kidney transplants, they pooled together related and unrelated living donor kidney recipients [23–28]. Our data show that 69% of all living donor kidney transplants in the United States come from

Table 3. Matched cohorts Marginal Cox Model for patient survival in unrelated living donor kidney transplants.

Parameter	*P* value	Hazard ratio	95% Confidence interval	
Zero-HLA mismatches versus >0 HLA mismatches	0.3459	1.430	0.680	3.011
Recipient age at time of transplant	0.0087	1.031	1.008	1.056
Black recipient	0.7858	0.862	0.296	2.513
Female recipient	0.1950	0.656	0.347	1.241
Final peak PRA ≥80 v. <80	0.1047	2.426	0.832	7.074
Biopsy proven acute rejection	0.9124	1.061	0.369	3.055
Induction with a lymphocyte depleting agent	0.0124	0.443	0.234	0.838
DM as primary cause of ESRD	0.0890	1.597	0.931	2.741
Dialysis <2 years versus no dialysis	0.8486	0.944	0.525	1.700
Dialysis ≥2 years versus no dialysis	0.1946	1.591	0.789	3.211

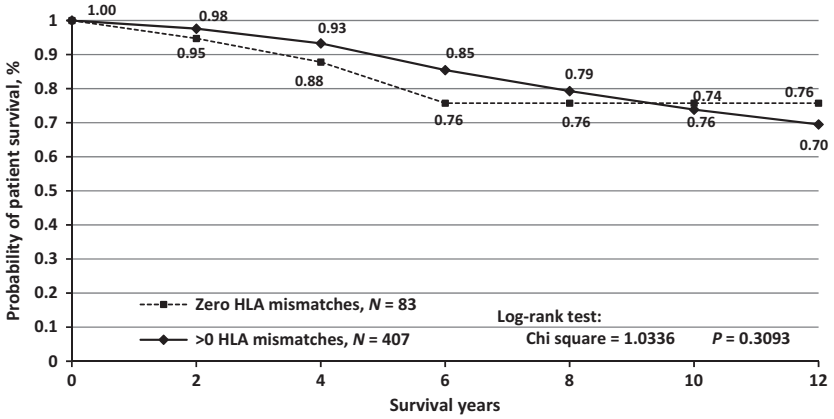

Figure 2 Matched cohorts Kaplan–Meier curves for patient survival in unrelated living donor kidney transplants, zero-HLA mismatches versus >0 HLA mismatches.

related donors, so the survival benefit previously reported with zero-HLA mismatched living donor kidney transplants may reflect the survival benefit in only *related* living donor kidney transplants (Figures 4 and 5). This makes sense as we would expect almost all zero-HLA mismatched transplants from a related living donor would be two haplotype matched as well. This genetic situation confers the best graft survival potential, aside from an identical twin donor, as not only are the 6 classically identified HLA antigens identical, but also other undocumented major and minor histocompatibility antigens.

A primary justification for prioritizing zero-HLA mismatches in a KPD matching algorithm was the assumption that it would promote better graft survival, similar to what is seen with the national sharing of zero-HLA mismatched *deceased* donor kidney transplants in the United States. Prior to our study, this was an understandable assumption, but now our study is the first to call into question that assumption's universal validity. Perhaps, better tissue quality in unrelated living donor transplants obviates the beneficial effect of zero-HLA mismatching seen in *deceased* donor transplants. But, only in *related* living donor transplants does the importance of zero-HLA mismatching re-emerge because zero-HLA mismatching serves as a surrogate term for a two haplotype matched transplant. One retrospective single center study hinted at the ineffectiveness of 6 antigen HLA matching in *unrelated* living donor kidney transplant recipients when no difference in graft survival was observed between groups of 0–1, 2–4, and 5–6 HLA mismatched transplants [32]. However, that study did not independently analyze zero-HLA mismatched unrelated living kidney transplants.

A possible disadvantage of prioritizing zero-HLA mismatches in the KPD allocation algorithm is that it may limit access to compatible matches for other potential recipients. For example, the current operational guidelines for the OPTN/UNOS Kidney Paired Donation Pilot Program (Interim Implementation, Version 6.0, effective December 2013) assigns 200 prioritization points for zero-HLA mismatches but only 0.07 points per day a potential recipient waits in its KPD program [29]. In other words under these guidelines, a zero-HLA mismatch prioritization

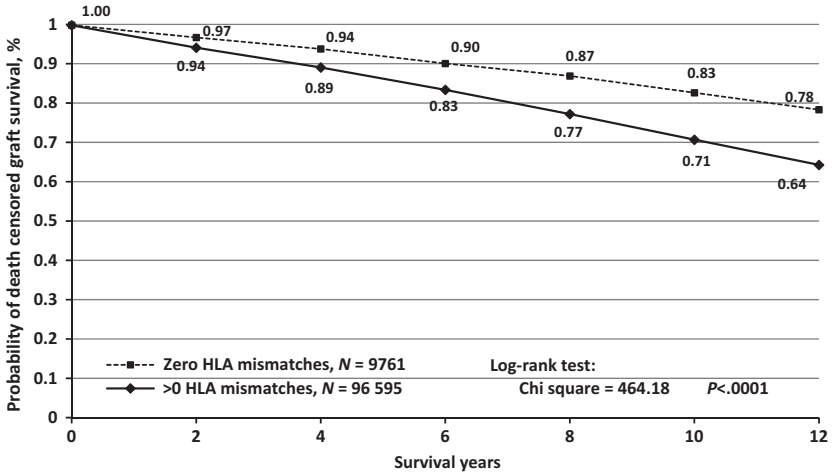

Figure 3 Kaplan–Meier curves for death-censored graft survival, all living donor kidney transplants—Includes Related, Unrelated, and Unknown donor–recipient relationships.

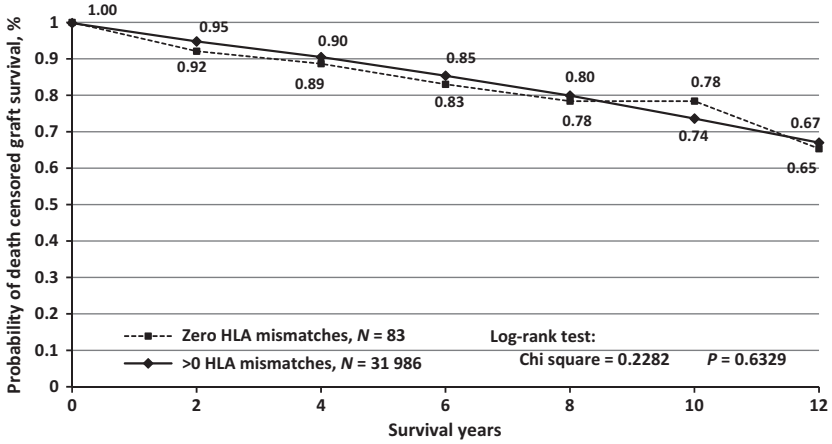

Figure 4 Kaplan–Meier curves for death-censored graft survival in all unrelated living donor kidney transplants, zero-HLA mismatches versus >0 HLA mismatches

is equivalent to 7.8 years of KPD waiting time. This would be another reason for rethinking the current 6 antigen, zero-HLA mismatching priority. However, it is not known whether zero-HLA mismatching in a KPD matching algorithm may increase access to transplantation in very highly sensitized patients (conference call with Dr. John Friedewald, March 7, 2014). For example, Stegall and colleagues analyzed the OPTN/UNOS database and reported that in the era of national sharing of zero-HLA mismatched *deceased* donor kidneys, 47% of the kidneys transplanted in patients with a panel reactive antibody of more than 80% were from zero-HLA mismatched deceased donors [20]. Unfortunately, verification in the context of KPD is outside the scope of this study. In our study cohort of zero-HLA mismatched unrelated living donor kidney recipients, only four patients were identified as having received KPD transplants.

It is worth noting that in Eurotransplant, the Acceptable Mismatch program was created as an alternative kidney allocation system to offset the matching disadvantage in highly sensitized patients [33]. If future studies verify our study's hypothesis, then—akin to the Eurotransplant Acceptable Mismatch program—it might be reasonable to consider alternative rules for KPD allocation in highly sensitized patients. For example, one might suggest that the zero-HLA mismatch priority could be kept intact for highly sensitized patients to offset their matching disadvantage, but discarded for the remaining patients who have a good chance of being matched in a reasonable period of time. At this point, this is speculation and we acknowledge the need

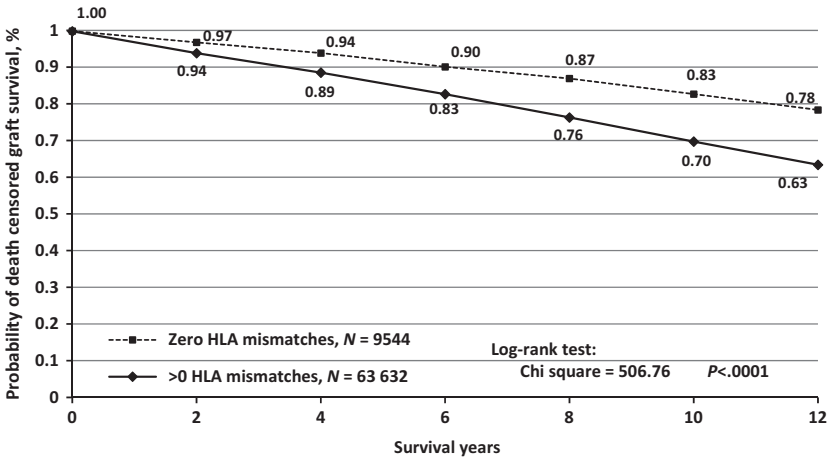

Figure 5 Kaplan–Meier curves for death-censored graft survival in all related living donor kidney transplants, zero-HLA mismatches versus >0 HLA mismatches.

for more corroborative data first, but it does illustrate a potential model to address inequalities in KPD organ allocation in highly sensitized patients.

Although no graft or patient survival benefit was seen in our study, it may not necessarily mean that we should discount the endeavor of HLA matching altogether. As mentioned previously, a graft survival benefit is seen with zero-HLA mismatched *related* living donor transplants probably because they are well matched at several nontraditional major and minor histocompatibility antigens. Perhaps what recipients of *unrelated* living donor transplants require is a more complete HLA matching of the nontraditional major and minor histocompatibility antigens. Unfortunately, our study's SRTR data were limited to reporting the traditional 6 major histocompatibility antigens. But, the OPTN/UNOS Paired Donation Pilot Program is already considering a policy to include additional typing for several nontraditional HLA antigens [29]. Also, there may be other potential benefits to zero-HLA mismatching besides graft and patient survival. In young unsensitized transplant recipients, a potential long-term benefit of zero-HLA mismatching may be that it keeps the risk of post-transplant sensitization low, therefore should the graft fail then the pool of potential donors stays open [30,34].

The strengths of our study are that we analyzed a large national database that included over 100,000 living donor kidney transplants and there was very little missing data. We found that 99% of living donor kidney transplants had their donor relationship available, and 98% of unrelated living donor kidney recipients had their HLA status available. Another strength is that our study is the first to report outcomes of zero-HLA mismatched kidney transplants from unrelated living donors—the same donor source used for KPD transplants. A limitation of the study is the confidence interval for death-censored graft survival which may imply a power issue; however, we feel this is reasonable in view of the low incidence of zero-HLA mismatched unrelated living donor transplants observed in a large national database. Another limitation is that it is a retrospective cohort analysis so only associations—not causations—can be made. However, a prospective study would be difficult to conduct because of the relative infrequency of cases and it would require an extended follow-up period.

In conclusion, our data suggest that in unrelated living donor kidney transplants, zero-HLA mismatching of the traditional 6 major histocompatibility antigens may not offer any benefit in death-censored graft or patient survival as previously assumed. As a result, our study brings zero-HLA mismatching to the forefront of the KPD allocation debate. But for potential KPD recipients, it is unclear whether removing the zero-HLA mismatch priority may have unfavorable consequences on select patient groups like highly sensitized patients. Therefore, particular study of the effect of zero-HLA mismatching in the context of KPD is needed to validate its allocation priority in the OPTN/UNOS Kidney Paired Donation Pilot Program.

Authorship

MJC: designed research/study. XW and MJC: performed research/study. XW: collected data. MJC, XW, SR, AHS and KAA: analyzed data. MJC and KAA: drafting manuscript. MJC, XW, SR, AHS and KAA: critical revision of manuscript.

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Other disclosures

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Kaplan–Meier curves for death-censored graft survival in all zero-HLA mismatched living donor kidney transplants, related donors versus nonrelated donors.

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