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Graft and patient outcomes of zero-human leucocyte-antigen-mismatched deceased and live donor kidney transplant recipients

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Summary

Greater compatibility of human leucocyte antigen (HLA) alleles between kidney donors and recipients may lead to improved graft outcomes. This study aimed to compare the incidence of acute rejection and graft failure in zero-HLA-mismatched recipients of living-related (LD) and deceased donor (DD) kidney transplants. Using data from the Australia and New Zealand Dialysis and Transplant Registry, we compared the risk of any acute rejection and biopsy-proven acute rejection (BPAR) and graft failure in recipients of zero-HLA-mismatched kidneys between LD and DD using logistic and Cox regression models. Of the 931 zero-HLA-mismatched recipients transplanted between 1990 and 2012, 19 (2.0%) received kidneys from monozygotic/dizygotic twins (twin), 500 (53.7%) from nontwin LD and 412 (44.3%) from DD. Twin kidney transplant recipients did not experience rejection. Compared to DD transplant recipients, the risk of any acute rejection (adjusted odds ratio 0.52, 95%CI 0.34–0.79, $P = 0.002$) and overall graft failure (adjusted hazard ratio 0.55, 95%CI 0.41–0.73, $P < 0.001$) was significantly lower in LD recipients independent of initial immunosuppression, but not for BPAR (adjusted odds ratio 0.52, 95%CI 0.16–1.64, $P = 0.263$). Zero-HLA-mismatched DD kidney transplant recipients have a significantly higher risk of any acute rejection episodes and graft loss compared to zero-HLA-mismatched LD kidney transplant recipients. A cautious and careful approach in reducing immunosuppression appears to be warranted in this group of transplant recipients.

Introduction

Immunological compatibility between donor and recipient is a major factor in determining graft outcomes in kidney transplantation [1–3]. The half-lives of allografts received from donors who exhibit zero-HLA mismatches with their recipients at the major class I (HLA-A and HLA-B) and class II (HLA-DR) loci were up to twice that of mismatched allografts among recipients of deceased donor (DD, 17 years vs. 8 years) [4] and live donor (LD, 22 years vs. 12–14 years) kidney transplants [5]. As a result, immunological matching at the HLA-A, HLA-B and HLA-DR loci

remains an important determinant of donor selection from LD and allocation of kidneys from DD for transplantation.

Compared with recipients of mismatched DD transplants, recipients of mismatched LD kidney transplants have better overall and death-censored graft survival [6]. In Australia, the overall 5-year graft survival was 89% among recipients of primary LD kidneys, compared to 81% among recipients of primary DD kidneys [7]. The rationale for the difference in outcomes is multifactorial, but may include shorter ischaemic time and duration on dialysis among LD kidney recipients.

Even among recipients of zero-HLA-mismatched LD kidney transplants, it has been shown that high levels of panel reactive antibodies (PRA) levels are important determinants of graft loss [8]. Recipients of LD-related, zero-HLA-mismatched transplants may be expected to exhibit superior graft and patient outcomes when compared to recipients of zero-HLA-mismatched DD kidneys because of the generally better outcomes associated with LD transplantation, coupled with better matching at the major and minor HLA alleles [9]. However, evidence supporting this hypothesis is contradictory [10,11]. In this study, we aimed to compare the incidence of acute rejection, graft failure and mortality between recipients of zero-HLA-mismatched kidneys transplanted from LD-related versus DD using data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

Materials and methods

Study population

All zero-HLA-mismatched LD and DD kidney transplant recipients in Australia and New Zealand between 1990 and 2012 were included in the analyses. We excluded recipients of multiple organ grafts and zero-HLA-mismatched LD-unrelated kidney transplant recipients ($n = 7$). Kidney transplant recipients were stratified into three groups depending on donor types – zero-HLA-mismatched monozygotic or dizygotic twin transplants (twin), zero-HLA-mismatched non-monozygotic or dizygotic twin LD-related transplants (LD-related) and zero-HLA-mismatched DD transplants (DD).

Data collection

Recorded baseline data included donor characteristics including age and gender. Recipients' baseline data included age, gender, race (Indigenous and non-Indigenous), cause of end-stage kidney disease (ESKD) (categorized as diabetic nephropathy, glomerulonephritis, cystic disease, vascular/hypertensive disease or others), pre-emptive transplantation, dialysis duration pretransplant (categorized as 0–1 year, >1–3 years, >3–5 years and >5 years on dialysis), diabetes, coronary artery disease (CAD) and smoking history (categorized as current smokers, former smokers or nonsmokers). Transplant-related characteristics included the use of induction antibody therapy (interleukin-2 receptor antibody or T-cell-depleting antibody), peak PRA levels (categorized as 0–10%, 11–50% and >50%), number of grafts, total ischaemic time, any rejection episodes, transplant era and type of immunosuppressive agents. Baseline immunosuppressive agents were categorized as CNI (none, cyclosporine, tacrolimus, CNI and mammalian target of rapamycin inhibitors [mTORi] or mTORi alone), antimetabolite (none, azathioprine or mycophenolic acid) and prednisolone.

Clinical outcomes

The primary clinical outcomes of this study were any acute rejection or biopsy-proven acute rejection (BPAR), overall graft failure (defined as death or returned to dialysis), death-censored graft failure (DCGF) and all-cause mortality. Data on the incidence of any acute rejection were collected from 1997. The reporting of acute rejection is voluntary, with majority being BPAR and coded as types of rejection (cellular, glomerular or vascular). The outcome data of all recipients were censored at 31 December 2012.

Statistical analyses

Comparisons of baseline characteristics between recipients stratified by donor types were made by chi-square test and analysis of variance (ANOVA) for categorical and continuous variables, respectively. The risk factors for any acute rejection or BPAR were assessed using multivariate logistic regression analysis. Graft and patient survivals were examined using Cox proportional hazard regression analysis. Results were expressed as hazard ratio (HR) or as odds ratio (OR) with 95% confidence interval (CI). The covariates included in the logistic regression and Cox regression models were donor characteristics (age and gender); recipient characteristics (including age, race, gender, cause of ESKD, pre-emptive transplantation, dialysis duration pretransplant, diabetes, smoking history and CAD) and transplant-related characteristics (including induction therapy, PRA level, number of grafts, total ischaemic time, rejection, transplant era and type of immunosuppressive agents). Effect modification between donor types with covariates and outcomes were examined. Variables that had an association with clinical outcomes with P-values of <0.20 in the unadjusted analyses were included in the multivariable-adjusted analyses. All analyses were undertaken using SPSS V10 statistical software program (SPSS Inc., North Sydney, Australia) and SAS statistical software 9.4.

Results

Study population

Table 1 shows the baseline characteristics of the study population stratified by donor types. There were 931 zero-HLA-mismatched kidney transplant recipients between 1990 and 2012 followed up for a median of 8.3 years (range 0.01–23.0 years) resulting in 8,458 person-years. Nineteen were (2.0%) twin transplants, 500 (53.7%) were LD-related, and 412 (44.3%) were DD transplants with median (interquartile range) follow-up period of 8.9 (2.1–14.3), 8.6 (4.2–13.4) and 8.0 (3.9–12.7) years, respectively. A total of 114 (12.2%) recipients experienced acute rejection, 274 (29.2%) experienced graft loss, and 177 (18.9%) died. Compared to DD transplant recipients, twin and LD-related transplant recipients were younger and spent less time on dialysis prior to transplantation with over 20% receiving pre-emptive kidney transplants. Over 50% of ESRD in twin transplants were attributed to glomerulonephritis compared to 47% and 40% in LD-related and DD transplants, respectively. DD transplant recipients were more likely to have a PRA level >50% compared to twin and LD-related transplant recipients (26%, 0% and 15% respectively, $P < 0.001$). Three (15%) twin transplant recipients did not receive either CNI or prednisolone at the time of transplantation. Twenty-three recipients (1 twin, 20 LD-related and 2 DD transplant recipients) received only a single immunosuppressive agent at the time of transplantation, with 20 (87%) recipients receiving either cyclosporin or tacrolimus alone, one recipient receiving prednisolone alone, one receiving mycophenolic acid alone and one recipient receiving azathioprine alone. One hundred and sixteen recipients (4 twin, 55 LD-related and 57 DD transplant recipients) received two agents at the time of transplantation: 60 (52%) recipients received a combination of CNI and prednisolone, 50 (43%) received CNI and antimetabolite, and 6 (5%) received antimetabolite and prednisolone.

A greater proportion of DD transplant recipients experienced any acute rejection episodes (15.8%, 0.0% and 9.6%, respectively; $\chi^2 = 10.76$, $P = 0.005$), BPAR (8.0%, 0.0% and 6.0%, respectively; $\chi^2 = 3.10$, $P = 0.376$), graft loss (40.0%, 21.1% and 21.0%, respectively; $\chi^2 = 40.12$, $P < 0.001$) and death (30.1%, 10.5% and 10.2%, respectively; $\chi^2 = 58.98$, $P < 0.001$) compared to twin and LD-related transplant recipients.

Donor types and acute rejection

Compared to DD transplant recipients, the overall risk of acute rejection was significantly lower in LD-related transplant recipients (adjusted OR 0.52, 95%CI 0.34–0.79, $P = 0.002$), independent of peak PRA, age and era (Fig. 1). Risk of antibody-mediated acute rejection was significantly greater for DD than for LD recipients (13.8% and 4.2%, respectively, χ^2 15.42, $P = 0.004$), and whilst a similar trend was evident for other subclasses of acute rejection, the differences were not individually significant: acute cellular (10.5% vs. 6.8%, respectively, χ^2 13.70, $P = 0.090$), glomerular (2.4% vs. 1.0%, respectively, χ^2 11.52, $P = 0.174$) and vascular rejection (13.4% vs. 2.0%, respectively, χ^2 10.60, $P = 0.226$). Donor type and transplant era were not effect modifiers between other covariates and the risk of acute rejection. Twin transplant recipients did not experience any rejection episodes. Sensitivity analysis restricting only to BPAR episodes ($n = 59$) showed a non-significant trend towards a lower risk of acute rejection in LD-related transplant recipients (adjusted OR 0.52, 95% CI 0.16, 1.64, $P = 0.263$) compared to DD transplant recipients.

Donor types and graft failure

The 1-year overall graft survivals for recipients of LD-related and DD transplant recipients were 97% and 91%, respectively, whereas the 5-year overall graft survivals were 90% and 81%, respectively (log-rank $P < 0.001$; Fig. 2). Compared with DD transplant recipients, the risk of overall graft failure was significantly lower in LD-related transplant recipients (adjusted HR 0.55, 95% CI 0.41–0.73, $P < 0.001$; Fig. 1). Increasing ischaemic time, current smokers, Indigenous recipients and earlier transplant eras were associated with an increased risk of overall graft failure. Donor type was not an effect modifier between other covariates and overall graft failure.

The 1-year death-censored graft survivals for LD-related and DD transplant recipients were 99% and 94%, respectively; whereas the 5-year death-censored graft survivals were 94% and 91%, respectively (log-rank $P = 0.573$). There was no association between donor types and risk of DCGF in the adjusted models (Fig. 1). Younger recipients, former/current smokers, Indigenous recipients and earlier transplant eras were associated with an increased risk of DCGF. Donor type was not an effect modifier between other covariates and DCGF. The various causes of graft failure are shown in Fig. 3. Chronic allograft nephropathy was the most frequent cause of graft failure in all groups (twins $n = 2$ [100%), LD-related $n = 32$ [44%] and DD $n = 44$ [51%]), followed by *de novo*/recurrent glomerulonephritis (twins $n = 0$ [0%), LD-related $n = 16$ [22%] and DD $n = 8$ [9%]) and vascular complications (twins $n = 0$ [0%), LD-related $n = 8$ [11%] and DD $n = 10$ [12%]; χ^2 13.7, $P = 0.189$). For live donor transplants, 50% of graft failure from recurrent disease was attributed to recurrent IgA nephropathy.

Table 1. Baseline characteristics of zero-human leucocyte antigen mismatch transplant recipients stratified by donor type.

	Donor types			
	Monozygotic twins (*n* = 19)	Live-related (*n* = 500)	Deceased donor (*n* = 412)	*P*-value
Donor				
Donor age (*n*, %)				
0–30	4 (21.1)	65 (13.0)	126 (30.6)	<0.001
>30–50	8 (42.1)	317 (63.4)	160 (38.8)	
>50	7 (36.8)	118 (23.6)	126 (30.6)	
Female (*n*, %)	11 (57.9)	264 (52.8)	187 (45.4)	0.130
Recipient				
Age (*n*, %)				
0–30	4 (21.0)	107 (21.4)	53 (12.9)	<0.001
>30–50	9 (47.4)	297 (59.4)	175 (42.5)	
>50	6 (31.6)	96 (19.2)	184 (44.6)	
Female (*n*, %)	10 (52.6)	212 (42.4)	185 (44.9)	0.752
Indigenous (*n*, %)	0 (0.0)	31 (6.2)	11 (2.7)	<0.001
Years on dialysis (*n*, %)				
0–1	14 (73.7)	251 (50.2)	69 (16.8)	<0.001
>1–3	3 (15.8)	130 (26.0)	138 (33.7)	
>3–5	2 (10.5)	28 (5.6)	81 (19.8)	
>5	0 (0.0)	91 (18.2)	122 (29.8)	
Cause of ESKD (*n*, %)				
Diabetes	2 (10.5)	26 (5.2)	34 (8.3)	<0.001
Glomerulonephritis	10 (52.6)	233 (46.6)	165 (40.0)	
Vascular	0 (0.0)	11 (2.2)	21 (5.1)	
Cystic	0 (0.0)	42 (8.4)	65 (15.8)	
Body mass index in kg/m^2 (*n*, %)				
0–20	3 (16.7)	51 (11.0)	35 (9.6)	0.065
>20–25	7 (38.9)	192 (41.6)	130 (35.8)	
>25–30	5 (27.8)	146 (31.6)	112 (30.9)	
>30	3 (16.7)	73 (15.8)	86 (23.7)	
Smoking history (*n*, %)				
Nonsmoker	11 (61.1)	286 (61.1)	223 (59.0)	0.753
Former smoker	6 (33.3)	133 (28.4)	116 (30.7)	
Current smoker	1 (5.6)	49 (10.5)	39 (10.3)	
Diabetes (*n*, %)	2 (11.1)	38 (7.6)	48 (11.9)	0.182
Coronary artery disease (*n*, %)	2 (11.1)	35 (7.0)	51 (12.7)	0.028
Peak PRA (*n*, %)				
0–10%	17 (89.5)	341 (68.8)	225 (54.9)	<0.001
11–50%	2 (10.5)	82 (16.5)	77 (18.8)	
>50%	0 (0.0)	73 (14.7)	108 (26.3)	
Pre-emptive transplant (n, %)	4 (21.1)	106 (21.2)	2 (0.5)	<0.001
Transplant				
Ischaemic time (mean, SD)	2.11 (1.33)	2.30 (1.52)	15.38 (4.78)	<0.001
First graft (*n*, %)	19 (100)	417 (83.4)	314 (76.2)	0.078
Transplant era (*n*, %)				
1990–1993	3 (15.8)	46 (9.2)	53 (12.9)	0.151
1994–1997	2 (10.5)	74 (14.8)	77 (18.7)	
1998–2001	4 (21.1)	95 (19.0)	75 (18.2)	
2002–2005	3 (15.8)	113 (22.6)	90 (21.8)	
2006–2009	1 (5.3)	105 (21.0)	70 (17.0)	
2010–2012	6 (31.5)	67 (13.4)	47 (11.4)	
Induction therapy (*n*, %)				
IL-2R antibody	5 (26.3)	141 (28.2)	132 (32.0)	0.06
T-cell-depleting antibody	0 (0.0)	12 (2.4)	28 (6.8)	0.008

Table 1. continued

	Donor types			
	Monozygotic twins (n = 19)	Live-related (n = 500)	Deceased donor (n = 412)	P-value
Initial CNI (n, %)				
None	3 (15.8)	3 (0.6)	8 (1.9)	<0.001
Cyclosporin	14 (73.7)	334 (66.8)	260 (63.1)	
Tacrolimus	2 (10.5)	161 (32.2)	113 (27.4)	
CNI + mTORi	0 (0.0)	2 (0.4)	27 (6.6)	
mTORi	0 (0.0)	0 (0.0)	4 (1.0)	
Initial antimetabolite (n, %)				
None	0 (0.0)	34 (6.8)	38 (9.2)	0.173
Mycophenolic acid	13 (68.4)	341 (68.2)	258 (62.6)	
Azathioprine	6 (31.6)	125 (25.0)	116 (28.2)	
Initial prednisolone (n, %)	16 (84.2)	442 (88.4)	401 (97.3)	<0.001
Rejection (n, %)	0 (0.0)	48 (9.6)	65 (15.8)	0.013

Data expressed as number (%) or as mean (standard deviation [SD]).
ESKD, end-stage kidney disease; HLA, human leucocyte antigen; PRA, panel reactive antibody; IL-2R antibody, interleukin-2 receptor antibody; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor.

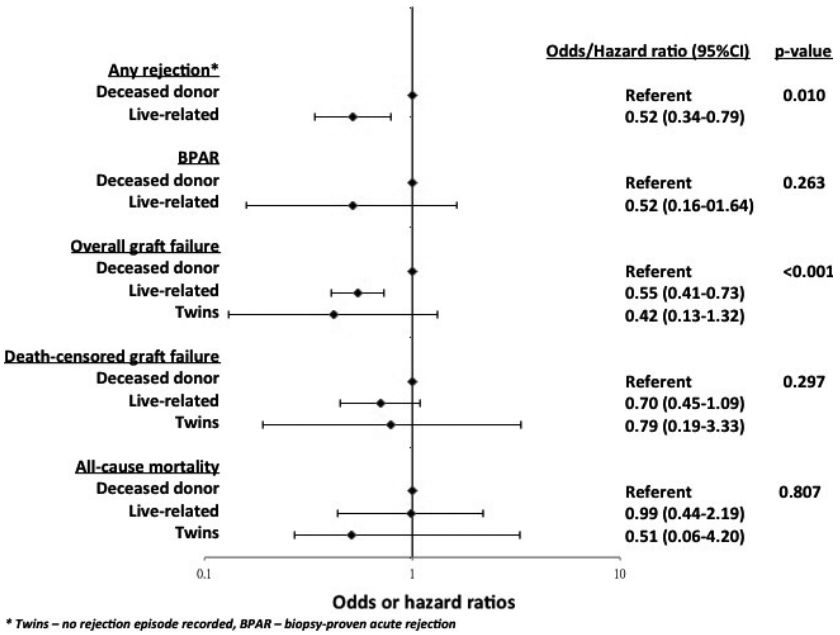

Figure 1 Donor types and adjusted odds or hazard ratios for rejection, overall graft failure, death-censored graft failure and all-cause mortality.

Donor types and all-cause mortality

The 1-year patient survivals for LD-related and DD transplant recipients were 98% and 97%, respectively, whereas the 5-year patient survivals were 96% and 89%, respectively, and 10-year patient survivals were 91% and 75%, respectively (log-rank $P < 0.001$, Fig. 4). Compared with DD transplant recipients, the risk of all-cause mortality was similar between twin transplant recipients (adjusted HR 0.51, 95% CI 0.06–4.20, $P = 0.528$) and LD-related transplant recipients (adjusted HR 0.99, 95%CI 0.44–2.19, $P = 0.972$; Fig. 1). Increasing ischaemic time, older recipients, pre-emptive transplants and increasing time on dialysis were associated with an increased risk of all-cause mortality. Donor type was not an effect modifier between other covariates and all-cause mortality. The various causes of all-cause mortality are shown in Fig. 3.

Discussion

We studied a cohort of 931 kidney transplant recipients of zero-HLA-mismatched LD-related and DD kidney

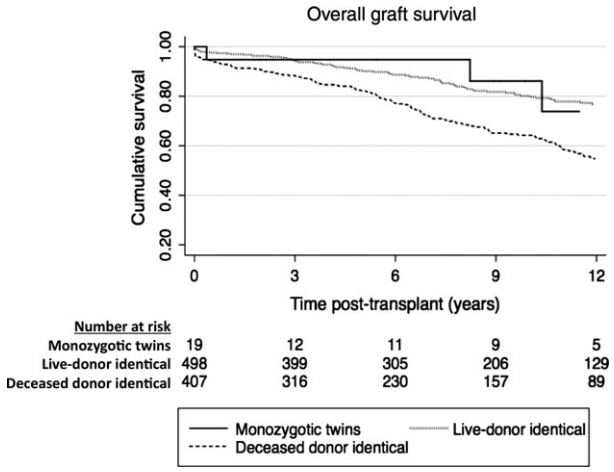

Figure 2 Unadjusted Kaplan–Meier survival curves for overall graft survival stratified by donor types (log-rank *P*-value <0.001).

transplants. DD recipients were found to incur a twofold increase in risks of any acute rejection and overall graft loss over LD-related recipients independent of age, time on dialysis, PRA and initial immunosuppression. However, when restricted to BPAR, there was a nonsignificant trend towards a higher risk of BPAR in DD recipients compared to LD-related recipients. The small group of mono- or dizygotic twins was free from rejection. Compared to mismatched recipients, a large proportion of zero-HLA-mismatched recipients received less intensive immunosuppression, particularly mono- or dual immunosuppressant therapy, which may have been contributory to the observed incidence of acute rejection and graft loss in zero-HLA-mismatched DD recipients.

A positive association between HLA mismatches and acute rejection risk in live and deceased donor kidney transplantation has been shown in previous studies [3]. In a retrospective study of 266 zero-HLA-mismatched sibling kidney transplants, lower incidences of both acute rejection (9% compared to 54%, respectively) and graft loss (5 years – 9% compared to 21%, respectively) were reported, as compared to HLA-mismatched sibling transplants [12,13]. Chronic allograft nephropathy and recurrent disease were the major causes of graft loss in zero-HLA-mismatched sibling kidney transplant recipients. Among a cohort of 4,048 zero-HLA-mismatched sibling kidney transplant recipients from the Collaborative Transplant Study, PRA level was positively and independently associated with increased risks of both acute rejection and graft failure [8]. These findings may suggest the importance of minor HLA antigenic mismatches and/or non-HLA immunity in predicting graft outcomes in kidney transplantation [8]. Compared to zero-HLA-mismatched LD-related kidney transplant recipients, a twofold increased risk of acute rejection and overall graft failure was observed among zero-HLA-mismatched DD transplant recipients in our study, although this association was not significant when restricted to BPAR. An increase in risk of antibody-mediated rejection, in

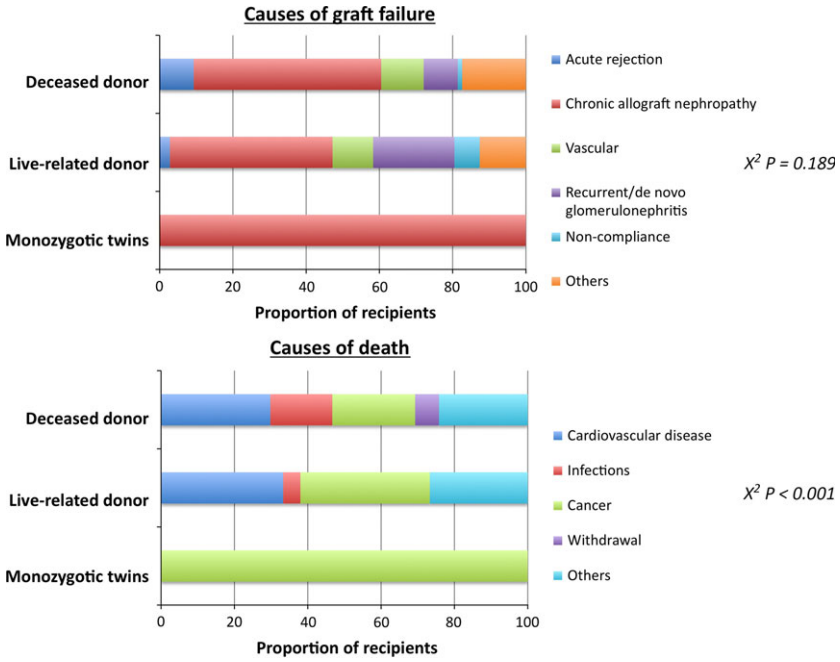

Figure 3 Causes of overall graft failure and death stratified by donor types.

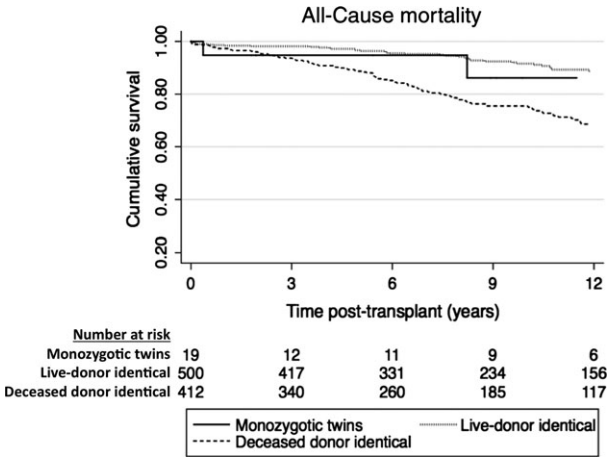

Figure 4 Unadjusted Kaplan–Meier survival curves for patient survival stratified by donor types (log-rank *P*-value <0.001).

particular, was evident. Potential mechanisms include the mismatch between splits of the apparently matched broad HLAs present in nonrelated zero-HLA-mismatched DD transplants [14], and potential mismatches at the HLA-Cw, HLA-DP and HLA-DQ loci and other mismatches of minor HLAs or non-HLAs. At present, mismatches at HLA-Cw, HLA-DP and HLA-DQ loci are not explicitly considered in donor kidney allocation in Australia and most other countries. The increased risk of graft failure but not DCGF among DD recipients was independent of acute rejection, but is likely to reflect the differences in residual confounding factors such as sensitisation status, rejection and duration of dialysis/likelihood of pre-emptive transplants known to be associated with graft loss [15,16].

Unlike previous studies [17–20], we were unable to show an association between acute rejection and graft survival. Varying patient characteristics, changes in immunosuppression used between eras, median follow-up of only 8 years and limited numbers likely restricted our power in this regard. Consistent with previous studies, recurrent familial forms of kidney disease were one of the predominant causes of graft failure in zero-HLA-mismatched LD kidney transplant recipients [19], particularly those with IgA nephropathy [21].

Even though zero-HLA-mismatched transplants are generally considered as low immunological risk, there is considerable variation in the use of immunosuppression. Of the 19 zero-HLA-mismatched twin transplant recipients in our study, 26% were initiated on single or dual immunosuppressive agents, typically a combination of CNI and corticosteroids. In contrast, less than 15% of zero-HLA-mismatched LD and DD kidney transplant recipients were initiated on single or dual immunosuppressive agents. Compared with standard practices in Australia and New Zealand, clinicians were less likely to prescribe induction therapy with interleukin-2 receptor antibody among recipients of low immunological risk. Between 2007 and 2011, 91% of kidney transplant recipients received an interleukin-2 receptor antibody [7], compared with approximately 30% in our zero-HLA-mismatched cohort. Other studies have shown that zero-HLA-mismatched LD kidney transplant recipients could be safely maintained on monotherapy with corticosteroids, CNI, antimetabolite or sirolimus; or dual therapy with CNI or antimetabolite with corticosteroids, although these regimens may be associated with an increased risk of *in vitro* donor-specific immune response of uncertain clinical significance with no apparent effects on graft or patient survivals [22–26]. There is a suggestion that zero-HLA-mismatched LD kidney transplant recipients maintained on CNI have a lower risk of rejection but at the expense of hypertension and a rapid decline in graft function compared to non-CNI regimens, but these findings have largely been derived from single-centre case series [23,27].

There is currently no general consensus with regard to the optimal induction and maintenance immunosuppression regimen in zero-HLA-mismatched kidney transplant recipients. The differences in rates of acute rejection and overall graft failure between zero-HLA-mismatched LD-related and DD kidney transplant recipients suggest that accurate assessment of extended immunological profiles, taking into consideration mismatches at other major and minor HLA loci and the presence and absence of donor-specific anti-HLA antibodies, nondonor specific anti-HLA antibodies and non-HLA antibodies, may be critical in individualizing the type and intensity of maintenance immunosuppression. Zero-HLA-mismatched twin and LD-related kidney transplant recipients may be successfully maintained on reduced intensity immunosuppression but the outcomes with the use of mono- or dual immunosuppressive agents will require close monitoring for longer-term outcomes to determine the effectiveness of these regimens. In contrast, our data suggest such reduced intensity immunosuppression in DD recipients may not be justified.

In the largest series of kidney transplant recipients of zero-HLA-mismatched monozygotic twins from the Organ Procurement Transplant Network, almost 30% of recipients were discharged on no immunosuppressive agents, with 66% immunosuppression-free at 12 months post-transplant [28]. Longer-term graft and patient outcomes of these recipients have not been reported. In another large series of 120 zero-HLA-mismatched twin donor kidney transplant recipients in the United States (United Network for Organ Sharing) and United Kingdom between 1988 and 2004, the 1- and 5-year graft survivals varied greatly between countries ranging from 99% and 89%, respec-

tively, in United States, compared to 83% and 75%, respectively, in United Kingdom [29]. The disparate survival rates between countries may reflect the differences in donor and recipient characteristics. Nevertheless, recipients of kidneys from mono- or dizygotic twins should be able to be maintained on reduced intensity immunosuppression but the choice of the type, number and intensity of immunosuppressive agents should be left to the discretion of the clinicians.

Our study has several strengths and limitations. This is the first study that has explicitly compared zero-HLA-mismatched LD with zero-HLA-mismatched DD kidney transplant recipients. The prospective nature and the completeness of the dataset suggest that selection and ascertainment biases in the exposure and study factors are minimized. Although multiple confounding factors were adjusted for, there may be unmeasured residual confounders such as the intensity of immunosuppression and presence of donor-specific anti-HLA antibodies, which are not collected by ANZDATA registry. Selection bias may exist because there may be systematic differences in the management of zero-HLA-mismatched kidney transplant recipients between transplanting centres and clinicians. In addition, the predominant use of low-resolution HLA typing during the study period may have resulted in the incorrect coding of HLA-mismatched LD and DD transplants as zero-HLA-mismatched transplants.

Conclusion

Zero-HLA-mismatched DD kidney transplant recipients incur a twofold increase in risk of any acute rejection episodes and overall graft failure, but exhibit similar rates of death-censored graft survival and patient survival compared to zero-HLA-mismatched LD-related kidney transplant recipients, independent of initial immunosuppression. Even though the association between donor types and rejection was no longer apparent when restricted only to BPAR, recipients of zero-HLA-mismatched grafts, with the exception of those between twins, are at risk of acute rejection and/or graft failure and clinicians should be cognizant of this in minimizing immunosuppression for these patient groups.

Authorship

WL, NG and GW: participated in the design and/or analysis of this study. All authors participated in the interpretation of data and drafting/revising the manuscript.

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References

1. Wissing K, Fomegné G, Broeders N, *et al.* HLA mismatches remain risk factors for acute kidney allograft rejection in patients receiving quadruple immunosuppression with anti-interleukin-2 receptor antibodies. *Transplantation* 2008; **85**: 411.
2. Beckingham I, Dennis M, Bishop M, Blamey R, Smith S, Nicholson M. Effect of human leucocyte antigen matching on the incidence of acute rejection in renal transplantation. *Br J Surg* 1994; **81**: 574.
3. Lim WH, Chadban SJ, Clayton P, *et al.* Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. *Clin Transplant* 2012; **26**: E428.
4. Takemoto S, Terasaki PI, Cecka JM, Cho YW, Gjertson DW. Survival of nationally shared, HLA-matched kidney transplants from cadaveric donors. The UNOS Scientific Renal Transplant Registry. *N Engl J Med* 1992; **327**: 834.
5. Gjertson DW, Cecka JM. Living unrelated donor kidney transplantation. *Kidney Int* 2000; **58**: 491.
6. Haberal M, Emiroğlu R, Başaran Ö, Tezel E, Karakayalý H, Bilgin N. Effects of HLA mismatching on graft survival in living donor-kidney transplantation. *Tissue Antigens* 2002; **60**: 556.
7. Clayton P, Campbell S, Chadban S, McDonald S, Hurst K. *Transplantation*. Adelaide, SA: Australia and New Zealand Dialysis and Transplant Registry, 2012.
8. Opelz G. Non-HLA transplantation immunity revealed by lymphocytotoxic antibodies. *Lancet* 2005; **365**: 1570.
9. Koo DD, Welsh KI, McLaren AJ, Roake JA, Morris PJ, Fuggle SV. Cadaver versus living donor kidneys: impact of donor factors on antigen induction before transplantation. *Kidney Int* 1999; **56**: 1551.
10. Jones JW Jr, Gillingham KJ, Sutherland DE, *et al.* Successful long-term outcome with 0-haplotype-matched living-related kidney donors. *Transplantation* 1994; **57**: 512.
11. Laging M, Kal-van Gestel JA, Haasnoot GW, *et al.* Transplantation results of completely HLA-mismatched living and completely HLA-matched deceased-donor kidneys are comparable. *Transplantation* 2014; **97**: 330.

12. Shimmura H, Tanabe K, Ishida H, *et al.* Long-term results of living kidney transplantation from HLA-identical sibling donors under calcineurin inhibitor immunosuppression. *Int J Urol* 2006; **13**: 502.
13. Peddi V, Bryant M, Roy-Chaudhury P, Woodle E, First M. Safety, efficacy, and cost analysis of thymoglobulin induction therapy with intermittent dosing based on CD3 + lymphocyte counts in kidney and kidney-pancreas transplant recipients. *Transplantation* 2002; **73**: 1514.
14. Opelz G. Importance of HLA antigen splits for kidney transplant matching. *Lancet* 1988; **2**: 61.
15. Kasiske BL, Snyder JJ, Matas AJ, Ellison MD, Gill JS, Kausz AT. Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol* 2002; **13**: 1358.
16. Lim W, Chapman J, Wong G. Peak panel reactive antibody, cancer, graft and patient outcomes in kidney transplant recipients. *Transplantation* 2014; DOI:10.1097/TP.0000000000000469 [Epub ahead of print].
17. McDonald S, Russ G, Campbell S, Chadban S. Kidney transplant rejection in Australia and New Zealand: relationships between rejection and graft outcome. *Am J Transplant* 2007; **7**: 1201.
18. Joseph JT, Kingsmore DB, Junor BJ, *et al.* The impact of late acute rejection after cadaveric kidney transplantation. *Clin Transplant* 2001; **15**: 221.
19. de Mattos AM, Bennett WM, Barry JM, Norman DJ. HLA-identical sibling renal transplantation–a 21-yr single-center experience. *Clin Transplant* 1999; **13**: 158.
20. Al-Kerithy M, Salazar A, Kiberd B, Bitter-Suermann H, MacDonald AS, Lawen JG. Impact of acute rejection on long-term graft survival in HLA-identical living-related kidney transplants. *Transplant Proc* 2001; **33**: 2982.
21. Feehally J, Farrall M, Boland A, *et al.* HLA has strongest association with IgA nephropathy in genome-wide analysis. *J Am Soc Nephrol* 2010; **21**: 1791.
22. Gerrits JH, van de Wetering J, van Beelen E, Claas FH, Weimar W, van Besouw NM. A multiplex bead array analysis to monitor donor-specific cytokine responses after withdrawal of immunosuppression in HLA-identical living related kidney transplant patients. *Transplant Proc* 2009; **41**: 1577.
23. MacDonald AS, Belitsky P, Bitter-Suermann H, *et al.* Long-term follow-up (5 and 10 years) in recipients of HLA identical living related donor kidney grafts receiving continuous cyclosporine compared with azathioprine. *Transplant Proc* 1997; **29**: 190.
24. Moon J, Kim Y, Chung S, Kim M, Kim S, Park K. Long-term results of kidney transplantation between HLA-identical siblings. *Surg Today* 2001; **31**: 123.
25. Keitel E, Santos AF, Alves MA, *et al.* Immunosuppression protocols for HLA identical renal transplant recipients. *Transplant Proc* 2003; **35**: 1074.
26. Venot M, Abboud I, Duboust A, *et al.* Calcineurin inhibitor-free monotherapy in human leukocyte antigen-identical live donor renal transplantation. *Transplantation* 2011; **91**: 330.
27. Sumrani N, Delaney V, Ding ZK, Butt K, Hong J. HLA-identical renal transplants: impact of cyclosporine on intermediate-term survival and renal function. *Am J Kidney Dis* 1990; **16**: 417.
28. Krishnan N, Buchanan PM, Dzebisashvili N, Xiao H, Schnitzler MA, Brennan DC. Monozygotic transplantation: concerns and opportunities. *Am J Transplant* 2008; **8**: 2343.
29. Kessaris N, Mukherjee D, Chandak P, Mamode N. Renal transplantation in identical twins in United States and United Kingdom. *Transplantation* 2008; **86**: 1572.