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Lifetime Risk of End-stage Kidney Disease in Living Donors for Pediatric Kidney Transplant Recipients in Australia and New Zealand

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LKD, living kidney donors; KTR, kidney transplant recipients; LKD-P, living kidney donors for pediatric kidney transplant recipients; LKD-A, living kidney donors for adult kidney transplant recipients; ESKD, end-stage kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; HLA, human leukocyte antigen; ANZDATA, Australia and New Zealand Dialysis and Transplant; uACR, urine albumin:creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; KPD, kidney paired donation; AKX, Australian Kidney Exchange; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IQR, interquartile range; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; SD, standard deviation

Conflict of interest:

The authors have no conflict of interest to declare.

Abstract

Living kidney donors (LKD) for pediatric kidney transplant recipients (KTR) have a heightened motivation to donate for emotional reasons and the clear health benefits to the KTR. We hypothesized that the cohort of LKD for pediatric KTR (LKD-P) includes motivated young parents with a higher lifetime end-stage kidney disease (ESKD) risk compared to adult KTR (LKD-A). Data from the Australia and New Zealand Dialysis and Transplant LKD Registry (2004-2015) was analysed to

compare baseline characteristics and pre-donation ESKD risk in LKD-P (n=315) versus LKD-A (n=3448). LKD-P were younger (median age 42 vs 50 years; *P*<0.001) and had a marginally higher lifetime ESKD risk (median 0.44% vs 0.40%; *P*<0.01), with a similar proportion of LKD exceeding 1% risk threshold (5.4% vs 5.6%; *P*=NS). Compared to grandparents as LKD-P, parents (median age 41 vs 59 years; *P*<0.001) had a higher lifetime ESKD (0.44% vs 0.25%; *P*<0.001). Although unique benefits to pediatric KTR justify the minor increase in lifetime ESKD risk in young parents, carefully selected grandparents are an alternative LKD-P option, allowing parents to donate for subsequent transplants.

Introduction

Kidney transplantation not only offers a survival advantage for children with end-stage kidney disease (ESKD) compared with remaining on dialysis (1, 2) but also unique benefits for growth (3) and cognitive development (4). Living kidney donors (LKD) facilitate timely (often pre-emptive) transplantation and superior outcomes over deceased donors (5). Therefore, young parents have heightened motivation to become LKD for their children. In an interdependent relationship, there are also tangible psychosocial benefits to parents as LKD after successful kidney transplantation (6). These benefits need to be balanced against the accumulating evidence for increased ESKD risk in LKD compared with healthy non-donors (7, 8). The recently published Kidney Disease Improving Global Outcomes (KDIGO) guideline (9) recommends the use of a multiparameter prediction tool such as the one developed by Grams et al (10) to estimate the lifetime pre-donation risk of ESKD, as well as an acceptance risk threshold of 1.0-1.5% (projecting to a post-donation risk of approximately 5%). However, parents as LKD for pediatric kidney transplant recipients (KTR) are usually younger with anticipated higher lifetime ESKD risk post-donation (11) for whom risk prediction may be imprecise, and risk factors poorly captured (12). This scenario presents a complex clinical scenario balancing optimal donor well-being, the emotional implications of parent-to-child donation and expected health benefits for the child with ESKD.

Pediatric KTR often have multiple LKD candidates, and the overwhelming majority will require re-transplantation later in their lifetime. Older grandparents are an alternative LKD option that mitigates the increased risk of ESKD in young parents as LKD and allows parents to donate for later subsequent re-transplantation if required. However, grandparents generally have inferior HLA matching, which increases the risk of broad sensitisation and compromises the prospects and outcome of re-transplantation (13). While the registry data are conflicting for older LKD offering either similar (14) or inferior (15) graft outcomes in the general adult KTR population, smaller studies have shown that carefully selected grandparents (16) and older LKD (17) may offer comparable graft outcomes for pediatric KTR.

To address these complex issues, we retrospectively compared baseline characteristics and ESKD risk profile of LKD for pediatric KTR (LKD-P) with those for adult KTR (LKD-A) using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry between 2004 and 2015. Pre-donation ESKD risk estimates were generated and compared using the prediction tool by Grams et al (10). We hypothesised that younger LKD-P with higher ESKD risk were more often accepted compared with LKD-A due to the unique benefits to pediatric KTR and parent LKD-P. The risk of ESKD and HLA mismatches from grandparents and parents for LKD-P were compared.

Materials and Methods

Study population

3969 LKD who donated between 2004 and 2015 were identified from the ANZDATA LKD Registry (http://anzdata.org.au), after excluding 10 non-directed altruistic LKD. Figure S1 illustrates those who were categorised into the *complete data cohort* (n=599, no missing baseline data, and all 10 variables within range for the ESKD risk calculation), and those who qualified for the *imputed data cohort* (n=3164). The imputed data cohort captured LKD with the 3 missing variables (urine albumin:creatinine ratio (uACR) and/or body mass index (BMI) and/or diabetes status), primarily due to unreported uACR. LKD from these two cohorts were then combined in the analysis. Those with the other 7 variables (age, gender, race, estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), anti-hypertensive requirement and smoking history) missing, or variables out of the risk calculation range, were excluded. This approach had been adopted for the original modelling of the ESKD risk calculator (10). Of the 3763 LKD in the combined cohort, 315 and 3448 were LKD-P (KTR age <18 years) and LKD-A (KTR age ≥18 years) respectively.

Data collection

In addition to the 10 above-mentioned variables, additional baseline demographic data were studied. These included LKD's relationship to KTR, diastolic BP (DBP), measured GFR (mGFR), KTR's age, and HLA mismatches (comparing direct donation from grandparent LKD-P versus parent LKD-P only). For LKD (n=164 (4.4%)) who participated in Kidney Paired Donation (KPD), the Australian Kidney Exchange (AKX) program database was linked with the ANZDATA registry, and baseline characteristics of the originally intended LKD (rather than the matched KPD LKD) were analysed. The relationship of the originally intended LKD with the KTR was not recorded. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to calculate eGFR. uACR is expressed as both mg/mmol and mg/g.

Estimation of pre-donation ESKD risk

Projected 15-year and lifetime pre-donation ESKD risk estimates were calculated by the prediction tool previously published (10), using an implementation in R (R Foundation for Statistical Computing,

Vienna, Austria). For the imputed data cohort, median values for missing uACR and/or BMI in LKD-A and LKD-P, and/or no diabetes for missing diabetes status, were imputed. For sensitivity analysis, either 75th percentile or 90th percentile values were imputed for missing uACR and/or BMI (Table S1). LKD of all non-white ethnicities (13.4%) in this study were considered as white for the purpose of risk calculation (Table 1).

Statistical analysis

Data analysis was performed using GraphPad Prism 7.02 (GraphPad, San Diego, CA, USA). Continuous variables were presented as median (interquartile range (IQR)), and comparisons between two groups were performed by two-tailed Mann-Whitney U-test. For HLA mismatches, data was also expressed as mean ± standard deviation (SD) and compared by unpaired t-test with Welch's correction. Categorical variables were presented as number (percentage of group) and compared by Fisher's exact test, or by multiple Chi-square tests for those with three or more mutually exclusive categories. A two-sided *p*-value of <0.05 was considered significant. Kernel density plots for comparison of age and ESKD risk distribution in different cohorts were generated using R and the ggplot2 package.

Results

Baseline demographics of LKD for pediatric versus adult KTR

LKD-P (n=315) compared to LKD-A (n=3448) were younger (Figure 1A), more likely to be <40 years of age, less likely to be ≥60 years of age, and less likely to be female (Table 1). LKD-P were primarily parents of the KTR (80.3% vs 20.6%), while 7.3% of the LKD-P were grandparents. LKD-P had less comorbidity, including lower SBP, DBP and anti-hypertensive requirement, higher eGFR and mGFR, but no differences in the proportion of LKD with BP ≥140/90 mmHg or mGFR ≤80 mL/min/1.73m^2. They were more likely to be current smokers, but not former smokers. Similar findings were observed from the complete data cohort, except a lack of differences in DBP and current smoking rate, and a lower rate of BMI ≥30 kg/m^2 in LKD-P (Table S2).

ESKD risk estimates

LKD-P compared to LKD-A had a significantly lower pre-donation 15-year but higher lifetime ESKD risk, however the absolute risk difference was minor (Table 2). The 90th, 95th and 98th risk percentile values (LKD with the highest 10%, 5% and 2% ESKD risk respectively) were similar. There was also no difference in the proportion of LKD exceeding the 1% or 2% lifetime ESKD risk threshold. Density plots of 15-year and lifetime risk estimates for the two groups virtually overlap (Figures 1B & C),

confirming that the differences were unlikely to be clinically relevant. Sensitivity analysis yielded similar findings although the differences in lifetime risk between the two groups were more accentuated (Table S3). In addition, it shows a larger proportion of LKD-P exceeding the 1% lifetime ESKD risk threshold compared with LKD-A.

Subgroup comparisons of age and ESKD risk of LKD for pediatric KTR

Grandparents versus Parents and Mothers versus Fathers as LKD

Pediatric KTR often have multiple LKD candidates. We analysed the ESKD risk and HLA mismatches from grandparents versus parents, and mothers versus fathers as LKD-P (Tables 3 and S4). Grandparents (n=23), compared to parents (n=253), donated to younger KTR (3 versus 12 years), were older (with almost half being ≥60 years of age) and had greater age mismatch (55 versus 31 years). Grandparents also had marginally higher 15-year but almost half the lifetime ESKD risk, with no grandparent LKD having a lifetime risk >1% (Table 3 and Figure 1D). They, however, had more comorbidity, including higher SBP, higher anti-hypertensive requirement, and lower eGFR and mGFR. Despite this, relatively few grandparent LKD-P had SBP ≥140 or required anti-hypertensives, and none had a mGFR <80 mL/min/1.73m^2 (Table S4).

Compared with fathers, mothers were of similar age but donated to older KTR with a lower age mismatch. This suggests that a proportion of mothers of childbearing age with younger KTR might have been excluded from donation. Alternatively, this may also reflect younger age of mothers compared to fathers. Mothers had lower 15-year and lower lifetime ESKD risk and were less likely to exceed the 1% lifetime risk threshold (Table 3). They also had lower SBP, DBP and BMI, and higher eGFR, reflecting less comorbidity (Table S4). Including grandparents in the comparison, the lifetime ESKD risk was lowest in grandparents followed by mothers, and highest in fathers (Table 3).

With regards to HLA mismatches, grandparents had higher A+B+DR and DR mismatches, and lower likelihood to achieve ≤3 A+B+DR mismatches compared with parents (Table 3). Despite this, over half of the grandparents as LKD had ≤3 A+B+DR mismatches, and there were no significant differences in the rates of zero A+B+DR or zero DR mismatch. As expected, there was no difference in HLA mismatches between mother and father LKD-P.

Age of pediatric KTR

Table S5 shows the LKD age, age mismatch between LKD and KTR, and ESKD risk stratified by the median pediatric KTR age (≤10 versus ≥11), for all LKD-P and for parent LKD-P only. Parent LKD for younger pediatric KTR were also younger, with 61.3% being <40 years of age. The age mismatch was however marginally greater, suggesting that some younger parents were declined as LKD. There

was a significantly lower 15-year but higher lifetime ESKD risk in parent LKD for younger pediatric KTR. The proportion of LKD exceeding the 1% or 2% lifetime ESKD risk threshold was similar.

Discussion

This study demonstrates that LKD-P had significantly lower 15-year but paradoxically higher lifetime pre-donation risk of ESKD compared to LKD-A. The lower 15-year risk likely reflects the LKD-P being primarily younger parents with fewer comorbidities, while the longer anticipated life expectancy would explain the consequent higher lifetime ESKD risk (11, 12). Although the differences were statistically significant, the absolute risk differences were minor. Therefore, any marginal increase in lifetime ESKD risk may be arguably outweighed by the benefits to the pediatric KTR and their parent LKD. There was no difference in the proportion of LKD-P exceeding the 1% or 2% lifetime pre-donation ESKD risk threshold, suggesting that similar acceptance criteria were used for LKD-P and LKD-A.

There are, however, limitations with the use of prediction tools for younger LKD. The modelling of these tools employed relatively short-term follow-up (10), while the incidence of ESKD only starts to rise exponentially from 10 years post-donation (18). Although KDIGO has proposed extrapolation of the post-donation ESKD risk by multiplying the pre-donation risk estimates by 3.5- to 5.3-fold (10), other studies have reported donation-attributable risk to be 8-to 11-fold (7, 8). Uncaptured risk factors such as family history and pre-diabetes likely further underestimate the post-donation ESKD risk. The imprecise risk prediction in younger LKD-P highlights the importance of long-term post-donation follow-up for early identification and optimisation of risk factors, as young motivated parents will likely continue to be the majority of LKD-P for their children.

Children with ESKD not uncommonly have multiple LKD candidates. The selection of the LKD should balance the risk to the LKD against that to the pediatric KTR. Since younger pediatric KTR had younger parents as LKD with attendant higher lifetime ESKD risk, grandparents would seem a reasonable alternative; however, this group consisted of only 7.3% of all LKD-P, similar to the International Collaborative Transplant Study (19). As grandparents tended to donate to younger pediatric KTR compared with parents, this would suggest that grandparents have already been used to mitigate risk to younger parents as LKD-P in Australia and New Zealand. Furthermore, as pediatric KTR likely require multiple transplants during their ESKD journey, one could argue for grandparents to be the first choice. This would allow younger parents to donate for subsequent transplants when their ESKD risk prediction improves in precision with advancing age. In small studies, grandparents (age 50-67) (16) and older LKD (age ≥50) (17) offered similar graft outcomes compared with parents and younger LKD respectively. However, caution should be exercised as grandparent LKD in these studies were likely a highly selected group with acceptable comorbidity profiles and HLA matching, as observed in our study. In addition, our cohort of grandparent LKD-P was relatively small.

Better HLA matching in pediatric KTR is associated with superior graft outcome, even in the contemporary era (17, 19). Recently, the combination of higher HLA eplet mismatch and poor adherence was found to synergistically worsen graft outcomes (20), a pertinent issue for pediatric KTR growing into adolescence and young adulthood. Furthermore, poor HLA matching for the first transplant is associated with broad HLA sensitisation, lower re-transplant rate and reduced re-graft survival (13), highly relevant for pediatric KTR requiring multiple transplants. There is also a risk of repeat HLA mismatches from grandparent LKD for the first transplant, and the development of specific alloimmunity may limit the prospect of one of the parents to become LKD for the second transplant. In this analysis, grandparents were more likely to have a higher HLA A+B+DR and DR mismatches compared with parents, but there were no significant differences in the rates of zero A+B+DR or DR mismatch. While all parent LKD-P would offer ≤3 A+B+DR mismatches (associated with superior graft survival compared with ≥4 A+B+DR mismatches (19)), over half of grandparent LKD-P also achieved this.

When challenged to balance the lifetime ESKD risk in a very young parent LKD candidate against the unfavourable HLA mismatch profile from a grandparent, a feasible option in some jurisdictions is for the grandparent LKD and pediatric KTR to participate in a KPD program as a quasi-compatible pair (21). This does not only offer the opportunity to improve the HLA mismatches but also increase the match rate for incompatible pairs in the program (22), a feasible option for pediatric KTR (23). It is, however, somewhat contentious to utilise KPD for reducing the donor/recipient age mismatch, and this is not presently permitted in some KPD programs.

Father LKD-P had both higher 15-year and lifetime ESKD risk compared to mother LKD-P. This was also observed in fathers and males in the LKD-A cohort compared with mothers and females, respectively (data not shown). It is thought that this reflects male gender as an independent risk factor for ESKD in both the non-donor (24) and LKD (25) populations, in addition to having more comorbidity. The lower ESKD risk in mothers as LKD-P needs to be balanced against the increased obstetric risk of pre-eclampsia and gestational hypertension for those of childbearing age yet to complete their family (26).

Our study has several important limitations. Despite the ANZDATA registry capturing all LKD in Australia and New Zealand over the 12 years studied, the sample size for LKD-P was modest, particularly when stratified for the subgroup analysis of grandparents. Due to missing data (primarily uACR), 85% of the included LKD required imputed values to generate ESKD risk estimates. However, the baseline characteristics and ESKD risk estimates of the imputed data and complete data cohorts were comparable (Table S2), and such an approach has been adopted in other studies (10, 27) to minimise selection bias and Type II errors. Furthermore, sensitivity analysis generated the consistent conclusion that LKD-P had a lower 15-year but higher lifetime ESKD risk, although the differences

were accentuated. The lifetime ESKD risk estimates using the imputed median values (Table 2) rather than the 75th and 90th percentile values (Table S3) would more likely reflect the actual risk, supported by Grams et al reporting that 6% of previous donors in the United States exceeded the 1% risk threshold (10). We acknowledge that a small proportion of LKD-P with missing uACR might have increased albuminuria and their consequent ESKD risk underestimated. However, any such potential underestimation should affect both LKD-P and LKD-A, as evidenced by the similar reported uACR values (Table 1). Finally, our study cohort was predominantly Caucasians and might not apply to other non-white ethnic groups at increased risk. For instance, African Americans have an approximate 4-fold increase in ESKD risk compared with white LKD (8). Despite these limitations, to our knowledge, this is the first novel study using national registry data to compare the pre-donation ESKD risk estimates to risk stratify the LKD-P sub-populations and highlight the influence of LKD age on lifetime ESKD.

In summary, LKD-P, primarily young parents, have a lower 15-year but higher lifetime ESKD risk. Although donor well-being remains a major clinical consideration, our study provides cautious reassurance that the absolute risk difference is minor. Furthermore, in the context of significant benefits to the pediatric KTR and emotional considerations, this small increased risk is likely outweighed by the unique relationship between the KTR and the parent LKD. To avoid the lifetime risk of ESKD in the very young parents as LKD, carefully selected grandparents should be considered as an alternative, and KPD might be a strategy to mitigate the immunologic risk to the pediatric KTR.

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Figure legends

Figure 1: Age and pre-donation ESKD risk in LKD.

Figures 1A-1D: Density plots of age (Figure 1A), 15-year (Figure 1B) and lifetime (Figure 1C) ESKD risk of LKD for pediatric versus adult KTR, and lifetime ESKD risk of parents versus grandparents as LKD for pediatric KTR (Figure 1D). Outliers with 15-year risk >0.75% (n=19) in Figure 1B and with lifetime risk >3% (n=7) in Figure 1C are not displayed.

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1: Schematic flow chart of the study cohorts.

Table S1: Imputed values of missing uACR and BMI using median, 75th and 90th percentile values for the imputed data cohort.

Table S2: Demographics and pre-donation risk estimates of LKD for pediatric versus adult KTR in compete data and imputed data cohorts.

Table S3: Sensitivity analysis of pre-donation ESKD risk estimates in LKD for pediatric versus adult KTR.

Table S4: ESKD risk profile of grandparent versus parent and mother versus father LKD for pediatric KTR.

Table S5: Demographics and pre-donation ESKD risk estimates of LKD for pediatric KTR stratified by median KTR age.

Tables

Table 1. Demographics of LKD for pediatric versus adult KTR

	LKD for Pediatric KTR (n=315)	**LKD for Adult KTR (n=3448)**	***P***
LKD age (years)	42 (37-49)	50 (42-58)	<0.001
Categorical LKD age (n (%))			<0.001
<40	120 (38.1%)	655 (19.0%)	
40-59	179 (56.8%)	2901 (60.6%)	
≥60	16 (5.1%)	702 (20.4%)	
Female gender (n (%))	163 (51.7%)	1991 (57.7%)	<0.05
Ethnicity (n (%))			0.41
White	272 (86.4%)	2985 (86.6%)	
Asian	16 (5.1%)	227 (6.6%)	
Australian indigenous	2 (0.6%)	13 (0.4%)	
Maori or Pacific Islander	10 (3.2%)	112 (3.2%)	
Other	14 (4.4%)	92 (2.7%)	
Not reported	1 (0.3%)	19 (0.6%)	

SBP (mmHg)	120 (110-130)	121 (115-130)	<0.001
≥140 (n (%))	26 (8.3%)	381 (11.0%)	0.15
DBP (mmHg)*	72 (69-80)	74 (70-80)	<0.05
≥90 (n (%))	12 (3.8%)	167 (4.8%)	0.49
Anti-hypertensive (n (%))	19 (6.0%)	335 (9.7%)	<0.05
BMI (kg/m^2)*	26.0 (23.6-28.5)	26.3 (23.8-29.0)	0.32
≥30 (n (%))	51 (16.2%)	619 (18.0%)	0.49
Smoking (n (%))	137 (43.5%)	1396 (40.5%)	0.35
Current	34 (10.8%)	232 (6.7%)	<0.05
Former	103 (32.7%)	1164 (33.8%)	0.76
Diabetes (n (%))*	2 (0.6%)	7 (0.2%)	0.17
eGFR (mL/min/1.73m^2)	98 (88-108)	92 (81-102)	<0.001
<80 (n (%))	36 (11.4%)	737 (21.4%)	<0.001
mGFR (mL/min/1.73m^2)*	118 (102-135)	109 (96-126)	<0.001
<80 (n (%))	3 (1.2%)	75 (2.8%)	0.15
uACR (mg/mmol)*	0.5 (0.3-1.0)	0.6 (0.3-1.1)	0.52
(mg/g)	4.4 (2.7-9.1)	5.3 (2.7-9.7)	
Relationship to KTR (n (%))			<0.001
Parent	253 (80.3%)	710 (20.6%)	
Grandparent	23 (7.3%)	6 (0.2%)	
Child	0 (0%)	171 (5.0%)	
Sibling	2 (0.6%)	801 (23.2%)	
Spouse	0 (0%)	849 (24.6%)	
Other - related	15 (4.8%)	195 (5.7%)	
Other – unrelated	14 (4.4%)	560 (16.2%)	
KPD	8 (2.5%)	156 (4.5%)	

LKD, living kidney donors; KTR, kidney transplant recipients; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; mGFR, measured GFR, uACR, urine albumin:creatinine ratio; KPD, kidney paired donation

*DBP – pediatric n=315, adult n=3447; BMI – pediatric n=302, adult n=3338; Diabetes – pediatric n=314, adult n=3422; mGFR – pediatric n=257, adult n=2721; uACR – pediatric n=68, adult n=546

Table 2. Pre-donation ESKD risk estimates in LKD for pediatric versus adult KTR

	LKD for Pediatric KTR (n=315)	LKD for Adult KTR (n=3448)	*P*
15-year ESKD risk			
Median (IQR) (%)	0.07 (0.05-0.11)	0.10 (0.07-0.16)	<0.001
Risk percentile (%)			
90th (highest 10% risk percentile)	0.17	0.23	
95th (highest 5% risk percentile)	0.23	0.30	
98th (highest 2% risk percentile)	0.38	0.42	
Lifetime ESKD risk			
Median (IQR) (%)	0.44 (0.31-0.63)	0.40 (0.26-0.59)	<0.01
Risk percentile (%)			
90th (highest 10% risk percentile)	0.88	0.84	
95th (highest 5% risk percentile)	1.08	1.03	
98th (highest 2% risk percentile)	1.49	1.30	
Proportion of LKD exceeding threshold (n (%))			
1% ESKD risk	17 (5.4%)	193 (5.6%)	>0.99
2% ESKD risk	2 (0.6%)	23 (0.7%)	>0.99

ESKD, end-stage kidney disease; LKD, living kidney donors; KTR, kidney transplant recipients; IQR, interquartile range

Table 3. Demographics, pre-donation ESKD estimates and HLA mismatches of grandparent versus parent and mother versus father LKD for pediatric KTR

	Grandparents (n=23)	Parents (n=253)	*P*	Mothers (n=124)	Fathers (n=129)	*P*
KTR age (years)	3 (2-7)	12 (6-15)	<0.001	12 (7-16)	10 (4-14)	<0.05
LKD age (years)	59 (55-65)	41 (37-47)	<0.001	41 (37-46)	42 (37-49)	0.07
Categorical LKD age (n (%))			<0.001			0.38
<40	0 (0%)	102 (40.3%)		53 (42.7%)	49 (38.0%)	
40-59	12 (52.2%)	150 (59.3%)		71 (57.3%)	79 (61.2%)	
≥60	11 (47.8%)	1 (0.4%)		0	1 (0.8%)	
Age mismatch (years)	55 (49-57)	31 (27-36)	<0.001	29 (25-34)	34 (29-37)	<0.001
15-year ESKD risk						
Median (IQR) (%)	0.11 (0.07-0.17)	0.07 (0.05-0.11)	<0.001	0.06 (0.04-0.07)	0.09 (0.06-0.13)	<0.001
Lifetime ESKD risk						
Median (IQR) (%)	0.25 (0.16-0.50)	0.44 (0.33-0.63)	<0.001	0.36 (0.28-0.47)	0.56 (0.41-0.78)	<0.001
Proportion of LKD exceeding threshold (n (%))						
1% ESKD risk	0 (0%)	20 (7.9%)	0.39	4 (3.2%)	16 (12.4%)	<0.01
2% ESKD risk	0 (0%)	2 (0.8%)	>0.99	1 (0.8%)	1 (0.8%)	>0.99

HLA mismatches*						
HLA A+B+DR mismatches						
Median (IQR)	3 (2-4)	2 (2-3)	<0.001	2 (2-3)	2 (2-3)	0.48
Mean ± SD	3.0 ± 1.3	2.2 ± 0.8	<0.05	2.2 ± 0.8	2.3 ± 0.8	0.53
0 mismatch (n (%))	1 (5.0%)	7 (3.1%)	0.50	4 (3.7%)	3 (2.1%)	0.16
≤3 mismatches (n (%))	11 (55.0%)	223 (100%)	<0.001	108 (100%)	115 (100%)	>0.99
HLA DR mismatches						
Median (IQR)	1 (1-2)	1 (0-1)	<0.01	1 (0-1)	1 (0-1)	0.14
Mean ± SD	1.1 ± 0.7	0.7 ± 0.5	<0.05	0.6 ± 0.5	0.7 ± 0.5	0.14
0 mismatch (n (%))	4 (20.0%)	74 (33.2%)	0.32	41 (38.0%)	33 (28.7%)	0.16

ESKD, end-stage kidney disease; LKD, living kidney donors; KTR, kidney transplant recipients; IQR, interquartile range; SD, standard deviation

*HLA mismatches – grandparents n=20, parents n =223, mothers n=108, fathers n=115

References

1. McDonald SP, Craig JC, Australian, New Zealand Paediatric Nephrology A. Long-term survival of children with end-stage renal disease. The New England journal of medicine. 2004;350(26):2654-62.

2. Van Arendonk KJ, Boyarsky BJ, Orandi BJ, James NT, Smith JM, Colombani PM, et al. National trends over 25 years in pediatric kidney transplant outcomes. Pediatrics. 2014;133(4):594-601.

3. Nissel R, Brazda I, Feneberg R, Wigger M, Greiner C, Querfeld U, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. Kidney international. 2004;66(2):792-800.

4. Hartmann H, Hawellek N, Wedekin M, Vogel C, Das AM, Balonwu K, et al. Early kidney transplantation improves neurocognitive outcome in patients with severe congenital chronic kidney disease. Transpl Int. 2015;28(4):429-36.

5. Australia and New Zealand Dialysis and Transplant Registry. Transplantation [Internet]. 2015 [Available from: http://www.anzdata.org.au/v1/report_2016.html.

6. Van Pilsum Rasmussen SE, Henderson ML, Kahn J, Segev D. Considering Tangible Benefit for Interdependent Donors: Extending a Risk-Benefit Framework in Donor Selection. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2017;17(10):2567-71.

7. Mjoen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Oyen O, et al. Long-term risks for kidney donors. Kidney international. 2014;86(1):162-7.

8. Muzaale AD, Massie AB, Wang MC, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. Jama. 2014;311(6):579-86.

9. Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberu J, Bakr MA, et al. Summary of Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors. Transplantation. 2017;101(8):1783-92.

10. Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. The New England journal of medicine. 2016;374(5):411-21.

11. Steiner RW. A Very Different Paradigm for Living Kidney Donor Risk. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2017;17(7):1701-2.

12. Lee D, Whitlam JB, Cook N, Manzoor M, Harley G, Choy SW, et al. Lifetime end-stage kidney disease risk estimation in living kidney donor candidates remains a challenge. Transpl Int. 2018;31(1):118-20.

13. Gralla J, Tong S, Wiseman AC. The impact of human leukocyte antigen mismatching on sensitization rates and subsequent retransplantation after first graft failure in pediatric renal transplant recipients. Transplantation. 2013;95(10):1218-24.

14. Chang P, Gill J, Dong J, Rose C, Yan H, Landsberg D, et al. Living donor age and kidney allograft half-life: implications for living donor paired exchange programs. Clin J Am Soc Nephrol. 2012;7(5):835-41.

15. Lim WH, Clayton P, Wong G, Campbell SB, Cohney S, Russ GR, et al. Outcomes of kidney transplantation from older living donors. Transplantation. 2013;95(1):106-13.

16. Simpson CM, McTaggart SJ, Sterne JA, Walker RG, Powell HR, Jones CL. Grandparent donors in paediatric renal transplantation. Pediatr Nephrol. 2005;20(11):1636-41.

17. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Relative importance of HLA mismatch and donor age to graft survival in young kidney transplant recipients. Transplantation. 2013;96(5):469-75.

18. Anjum S, Muzaale AD, Massie AB, Bae S, Luo X, Grams ME, et al. Patterns of End-Stage Renal Disease Caused by Diabetes, Hypertension, and Glomerulonephritis in Live Kidney Donors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2016;16(12):3540-7.

19. Opelz G, Dohler B, Middleton D, Susal C, Report ACTS. HLA Matching in Pediatric Kidney Transplantation: HLA Poorly Matched Living Donor Transplants Versus HLA Well-Matched Deceased Donor Transplants. Transplantation. 2017;101(11):2789-92.

20. Wiebe C, Nevins TE, Robiner WN, Thomas W, Matas AJ, Nickerson PW. The Synergistic Effect of Class II HLA Epitope-Mismatch and Nonadherence on Acute Rejection and Graft Survival. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(8):2197-202.

21. Cuffy MC, Ratner LE, Siegler M, Woodle ES. Equipoise: ethical, scientific, and clinical trial design considerations for compatible pair participation in kidney exchange programs. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2015;15(6):1484-9.

22. Ferrari P, Cantwell L, Ta J, Woodroffe C, D'Orsogna L, Holdsworth R. Providing Better-Matched Donors for HLA Mismatched Compatible Pairs Through Kidney Paired Donation. Transplantation. 2017;101(3):642-8.

23. Sypek MP, Alexander SI, Cantwell L, Ierino FL, Ferrari P, Walker AM, et al. Optimizing Outcomes in Pediatric Renal Transplantation Through the Australian Paired Kidney Exchange Program. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2017;17(2):534-41.

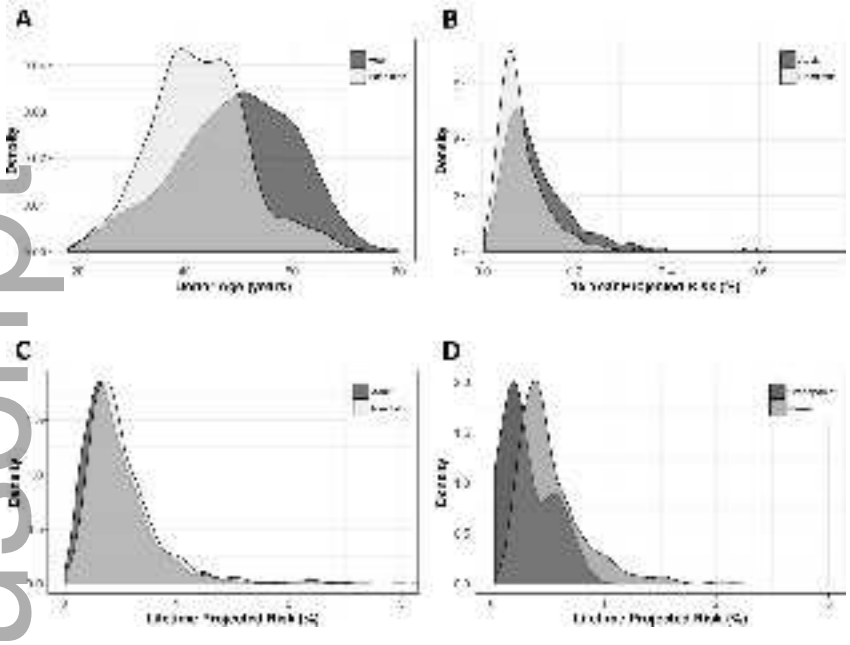
24. Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;62(2):245-52.

25. Massie AB, Muzaale AD, Luo X, Chow EKH, Locke JE, Nguyen AQ, et al. Quantifying Postdonation Risk of ESRD in Living Kidney Donors. Journal of the American Society of Nephrology : JASN. 2017.

26. Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, et al. Gestational hypertension and preeclampsia in living kidney donors. The New England journal of medicine. 2015;372(2):124-33.

27. Locke JE, Reed RD, Massie A, MacLennan PA, Sawinski D, Kumar V, et al. Obesity increases the risk of end-stage renal disease among living kidney donors. Kidney international. 2017;91(3):699-703.

Figure 1



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