Association of Primary Kidney Disease Type and Donor Relatedness With Live Donor Kidney Transplant Outcomes: An Analysis of ANZDATA

Dong Yu, Eva Malacova, Cameron Hurst, Monica Suet Ying Ng, and Andrew John Mallett

Rationale & Objective: There is limited information about the association between primary kidney disease and donor relatedness with transplant outcomes. This study addresses this gap by evaluating clinical outcomes after kidney transplantation in recipients of living donor kidneys as a function of primary kidney disease type and donor relatedness in Australia and New Zealand.

Study Design: Retrospective observational study.

Setting & Participants: Kidney transplant recipients who received allografts from living donors between January 1, 1998, and December 31, 2018, as recorded in the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA).

Exposures: Primary kidney disease type categorized as majority monogenic, minority monogenic, or other primary kidney disease based on disease heritability as well as donor relatedness.

Outcome: Primary kidney disease recurrence, graft failure.

Analytical Approach: Kaplan-Meier analysis and Cox proportion hazards regression to generate hazard ratios for primary kidney disease recurrence, allograft failure, and mortality. Partial likelihood ratio test was used to examine possible interactions between primary kidney disease type and donor relatedness for both study outcomes.

Results: Among 5,500 live donor kidney transplant recipients, majority monogenic (adjusted HR, 0.58, $P < 0.001$) and minority monogenic primary kidney diseases (adjusted HR, 0.64, $P < 0.001$) were associated with reduced primary kidney disease recurrence compared with other primary kidney diseases. Majority monogenic primary kidney disease was also associated with reduced allograft failure (adjusted HR, 0.86, $P = 0.04$) compared with other primary kidney diseases. Donor relatedness was not associated with primary kidney disease recurrence nor graft failure. No interaction was detected between primary kidney disease type and donor relatedness for either study outcome.

Limitations: Potential misclassification of primary kidney disease type, incomplete ascertainment of primary kidney disease recurrence, unmeasured confounding.

Conclusions: Monogenic primary kidney disease is associated with lower rates of primary kidney disease recurrence and allograft failure. Donor relatedness was not associated with allograft outcomes. These results may inform pretransplant counseling and live donor selection.

Visual Abstract online

Complete author and article information provided before references.

Correspondence to M.S.Y. Ng (monica.ng@health.qld.gov.au) or A.J. Mallett (andrew.mallett@health.qld.gov.au)

Am J Kidney Dis. 82(5):569-580. Published online June 27, 2023.

doi: 10.1053/j.ajkd.2023.04.004

Despite advances in dialysis technologies, kidney transplantation remains the optimal treatment for kidney failure in regards to survival and quality of life.[1] In 2019, the median waiting time for a deceased-donor kidney transplant was 2.1 years in Australia with more than 1,000 people actively awaiting kidney transplantation.[2] Live donor kidney transplants reduce the strain on deceased-donor wait lists and are linked to shorter dialysis vintage.[3,4] Furthermore, live donor kidney transplants are associated superior graft and recipient survival compared with deceased donor transplants.[3,4]

Editorial, p. 518

Globally, the majority of living kidney donors are biologically related to their recipient, which carries the benefit of improved human leukocyte antigen (HLA) matching but theoretically increases the risk of primary kidney disease recurrence.[5] Familial clustering of kidney disease has been observed across multiple population-level cohorts, where people with first-degree relatives with kidney failure experience up to 7.2 times increased risk of kidney failure, regardless of etiology.[6-8] It follows that shared genetic factors may increase the risk of primary kidney disease recurrence, particularly if the donor is closely related to the recipient. Recent advances in genetic kidney disease diagnosis have significantly reduced primary kidney disease recurrence for monogenic kidney diseases because these diseases can be identified either genetically or clinically on predonation screens.[9] The effect of unrecognized shared genetic factors on live donor kidney transplant outcomes, particularly primary kidney disease recurrence and graft failure, remains unclear.

Furthermore, there is limited high-resolution information about live related and unrelated donor kidney transplant outcomes in the modern era. The shortcomings of the published literature include (1) a primary focus on spousal live donor transplants,[10-12] (2) a lack of control for HLA matching,[13-15] (3) inclusion of participants from the pre–Efficacy Limiting Toxicity Elimination (ELITE) Symphony trial era,[16] and (4) limited investigation of primary kidney disease recurrence. Our study addresses these issues by exploring the

PLAIN-LANGUAGE SUMMARY

There are theoretical concerns that live-donor kidney transplants may be associated with increased risks of kidney disease recurrence and transplant failure due to unmeasurable shared genetic factors between the donor and the recipient. This study analyzed data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry and showed that, although disease type was associated with the risk of disease recurrence and transplant failure, donor relatedness did not impact transplant outcomes. These findings may inform pretransplant counseling and live donor selection.

associations of donor relatedness and primary kidney disease type with the clinical transplant outcomes of primary kidney disease recurrence and allograft failure.

Methods

Study Design and Setting

This retrospective observational cohort study included all first kidney recipients of live donor kidney grafts in Australia and New Zealand between January 1, 1998, and December 31, 2018. Deidentified information on recipient and donor factors, cold ischemia time, HLA matching, graft function, acute rejection, graft failure, and mortality were received from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. This study was approved by ANZDATA (42676) and the Metro North Health Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2019/QRBW/60194). The participants provided individual-level consent on entry into the ANZDATA registry for research approved by the ANZDATA steering committee and local HREC.

Study Variables

Types of primary kidney disease were categorized into majority monogenic, minority monogenic, and other primary kidney disease based on disease heritability (Table S1). Diseases were classified as majority monogenic for primary kidney disease when there was evidence from prior cohort/case series studies that ≥50% of cases have an identifiable monogenic basis. Diseases were classified as minority monogenic when there was evidence from prior cohort/case series studies that <50% of cases have an identifiable monogenic basis. Evidence was drawn from gene and primary kidney disease listings in Online Mendelian Inheritance in Man (www.omim.org). A monogenic basis was defined as a likely pathogenic or pathogenic (ACMG variant classification) variant or variants with the appropriate zygosity in a gene with an established or justified gene-phenotype/primary kidney disease relationship. Phenocopy disorders were excluded from the assessment of monogenic basis for primary kidney diseases, for example, disease-causing variants in COL4A3, COL4A4, or COL4A5 in the setting of apparent familial IgA nephropathy. Gene-phenotype relationships were drawn from Online Mendelian Inheritance in Man (www.omim.org), PanelApp Australia (https://panelapp.agha.umccr.org) and the ClinGen Clinical Domain Working Groups (https://clinicalgenome.org/working-groups/clinical-domain/clingen-kidney-disease-clinical-domain-working-group/). Donor relatedness was classified as immediate relative (identical twins and first degree), distant relative (second and third degree), and unrelated (other) (Table S2).

The covariates assessed included recipient age, sex, ethnicity, smoking status (current, former, never), comorbidities (chronic lung disease, coronary artery disease, peripheral vascular disease, cerebral artery disease, diabetes mellitus), and transplant era. Donor age, sex, and ethnicity were also assessed as covariates. Recipient and donor age in decades, HLA mismatch, cold ischemia time, and pretransplant dialysis vintage in months were included as a continuous variable. Recipient and donor ethnicity was categorized as white, Aboriginal and Torres Strait Islander (ATSI), Māori, Asian, and other in the descriptive statistics. In the Cox regression and competing risk analyses, ethnicity was included as white or other. Primary kidney disease recurrence, mortality, and graft failure were assessed as time-to-event variables. Primary kidney disease recurrence was defined as either primary kidney disease recurrence on biopsy or graft failure secondary to primary kidney disease recurrence. Graft failure was defined as events where the graft was no longer functioning (excluding death with functioning graft). In exploratory analyses, mortality as assessed as time-to-event variable.

Statistical Analyses

Baseline characteristics were reported using counts and percentages (Table 1 and 2). For continuous variables, analysis of variance (ANOVA) was used to compare the test variable (eg, recipient age) against the stratification variable (ie, primary kidney disease type or donor relatedness). We used a χ^2 test of independence for the categorical variables.

Kaplan-Meier survival curves were applied to evaluate the time from transplant to graft failure. Cox proportional hazards regression was used to calculate the unadjusted hazard ratio (HR) and adjusted HR (AHR) of primary kidney disease recurrence and graft failure. The 2 particular effects of interest, primary kidney disease heritability and donor relatedness, were forced into all multivariable models. Other covariates were retained in the final model if they represented important confounders (altered main effect sizes by >20%) or risk factors (statistically associated with the outcomes). Partial likelihood ratio test was used to test the interaction between primary kidney disease type and donor-relatedness, and its effects on primary kidney disease recurrence and graft failure. In terms of missing values, the analysis set employed was based on the type of analysis. For analyses considering bivariate associations,

Table 1. Clinical Characteristics of Living Kidney Transplantation Recipients and Donors by Primary Kidney Disease Type

Characteristics	Majority Monogenic (n = 1,030)	Minority Monogenic (n = 851)	Other Primary KD (n = 3,619)	*P* Value
Donor relatedness				<0.001[a]
Unrelated	601 (58.3%)	229 (26.9%)	1,434 (39.6%)	
Immediate relatives	370 (35.9%)	564 (66.3%)	2,020 (55.8%)	
Distant relatives	59 (5.7%)	58 (6.8%)	165 (4.6%)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Recipient age, y	46.70 ± 14.91	32.08 ± 16.98	42.95 ± 16.50	<0.001[a]
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Recipient sex				<0.001[a]
Female	422 (41.0%)	405 (47.6%)	1,257 (34.7%)	
Male	608 (59.0%)	446 (52.4%)	2,362 (65.3%)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	
Recipient ethnicity				<0.001[a]
Caucasian	943 (91.6%)	751 (88.2%)	2,841 (78.5%)	
Asian	26 (2.5%)	34 (4.0%)	391 (10.8%)	
ATSI	5 (0.5%)	5 (0.6%)	43 (1.2%)	
Maori	13 (1.3%)	15 (1.8%)	116 (3.2%)	
Pacific	14 (1.4%)	20 (2.4%)	112 (3.1%)	
Other	15 (1.5%)	17 (2.0%)	53 (1.5%)	
Missing	14 (1.4%)	9 (1.1%)	63 (1.7%)	
Recipient smoking status				<0.001[a]
Never	658 (63.9%)	616 (72.4%)	2,272 (62.8%)	
Former	306 (29.7%)	168 (19.7%)	1,035 (28.6%)	
Current	56 (5.4%)	61 (7.2%)	241 (6.7%)	
Missing	10 (1.0%)	6 (0.7%)	71 (2.0%)	
Recipient comorbidities				
Lung disease	28 (2.7%)	21 (2.5%)	203 (5.6%)	<0.001[a]
Coronary artery disease	92 (8.9%)	29 (3.4%)	418 (11.6%)	<0.001[a]
Peripheral vascular disease	23 (2.2%)	8 (0.9%)	214 (5.9%)	<0.001[a]
Cerebrovascular disease	49 (4.7%)	10 (1.2%)	138 (3.8%)	<0.001[a]
Diabetes mellitus	32 (3.1%)	18 (2.1%)	556 (15.4%)	<0.001[a]
HLA mismatch	3.36 ± 1.69	2.75 ± 1.53	2.99 ± 1.68	<0.001[a]
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cold ischemia time, h	2.98 ± 2.16	2.73 ± 1.80	2.85 ± 2.03	0.03[b]
Missing	23 (2.2%)	15 (1.8%)	82 (2.3%)	
Pre-emptive	381 (37.0%)	343 (40.3%)	989 (27.3%)	<0.001[a]
Dialysis vintage, mo	12.82 ± 19.79	11.95 ± 18.99	16.15 ± 22.46	<0.001[a]
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Donor age, y	49.67 ± 10.31	47.44 ± 11.11	48.66 ± 11.74	<0.001[a]
Missing	0 (0.0%)	1 (0.1%)	0 (0.0%)	
Donor sex				0.2
Female	531 (51.6%)	406 (47.7%)	1,888 (52.2%)	
Male	397 (38.5%)	331 (38.9%)	1,338 (37.0%)	
Missing	102 (9.9%)	114 (13.4%)	393 (10.9%)	
Donor ethnicity				<0.001[a]
Caucasian	764 (74.2%)	563 (66.2%)	2,373 (65.6%)	
Asian	28 (2.7%)	26 (3.1%)	190 (5.3%)	
ATSI	8 (0.8%)	18 (2.1%)	67 (1.9%)	
Maori	9 (0.9%)	13 (1.5%)	58 (1.6%)	
Pacific	3 (0.3%)	3 (0.4%)	30 (0.8%)	
Other	14 (1.4%)	11 (1.3%)	41 (1.1%)	
Missing	204 (19.8%)	217 (25.5%)	860 (23.8%)	

(Continued)

Table 1 (Cont'd). Clinical Characteristics of Living Kidney Transplantation Recipients and Donors by Primary Kidney Disease Type

Characteristics	Majority Monogenic (n = 1,030)	Minority Monogenic (n = 851)	Other Primary KD (n = 3,619)	*P* Value
Baseline immunosuppression				
Cyclosporin	426 (41.4%)	364 (42.8%)	1,634 (45.2%)	<0.001[a]
Tacrolimus	776 (75.3%)	670 (78.7%)	2,670 (73.8%)	0.01[b]
Azathioprine	150 (14.6%)	181 (21.3%)	614 (17.0%)	<0.001[a]
Mycophenolate	855 (83.0%)	728 (85.5%)	3,085 (85.2%)	0.2
Sirolimus	93 (9.0%)	88 (10.3%)	350 (9.7%)	0.6
Everolimus	90 (8.7%)	51 (6.0%)	199 (5.5%)	<0.001[a]
Prednisolone	1,019 (98.9%)	842 (98.9%)	3,577 (98.8%)	0.9
Primary KD recurrence	49 (4.8%)	51 (6.0%)	307 (8.5%)	<0.001[a]
Graft failure	132 (12.8%)	182 (21.4%)	627 (17.3%)	<0.001[a]
Graft failure cause[c]				0.6
Acute rejection	12 (9.1%)	15 (8.2%)	39 (6.2%)	
BKV nephropathy	4 (3.0%)	3 (1.6%)	18 (2.9%)	
De novo glomerulonephritis	4 (3.0%)	3 (1.6%)	25 (4.0%)	
Primary KD recurrence	4 (3.0%)	11 (6.0%)	54 (8.6%)	
Noncompliance	9 (6.8%)	15 (8.2%)	38 (6.1%)	
Vascular cause	7 (5.3%)	10 (5.5%)	30 (4.8%)	
Chronic nephropathy	80 (60.6%)	110 (60.4%)	370 (59.0%)	
Other	9 (6.8%)	12 (6.6%)	48 (7.7%)	
Missing	2 (1.5%)	3 (1.6%)	5 (0.8%)	
Transplant era				0.006[d]
1998-2003	161 (15.6%)	188 (22.1%)	709 (19.6%)	
2004-2008	264 (25.6%)	204 (23.9%)	885 (24.5%)	
2009-2013	337 (32.7%)	244 (28.7%)	1,031 (24.5%)	
2014-2020	268 (26.0%)	216 (25.4%)	994 (37.5%)	

Values for continuous variables given as mean ± SD; for categorical variables as number (percentage). Abbreviations: ATSI, Aboriginal and Torres Strait Islander; BKV, BK virus; HLA, human leukocyte antigen; HR, hazard ratio; KD, kidney disease.
[a]Significance level $P < 0.001$.
[b]Significance level $P < 0.05$.
[c]Graft failure cause percentages expressed as percentage of people with graft failure instead of total sample size.
[d]Significance level $P < 0.01$.

the available case set was used for each pairwise association whereas for multivariable modeling the complete case set was used.

Graft failure was also investigated as competing risks by generating subdistribution cumulative incidence functions and testing the differences between these incidence curves using the methods outlined by Fine and Gray.[17] Competing risk plots were generated to show cumulative incidence curves for mortality-censored graft failure. Right censoring was used when participants were censored if they died before developing graft failure. A significance level of 0.05 was used throughout all analyses. Statistical analyses were performed using R statistical package (v3.3, R Core Team, 2018).

Results

The study included 5,500 living donor kidney transplantations (Fig 1). The majority of the primary kidney diseases had no monogenic basis (n = 3,619; 65.8%) (Table 1). Of the transplants, 3,236 involved a living related donor, and 2,264 were living nonrelated donor (Table 2). More than half the transplants occurred between immediate relatives (n = 2,954; 53.7%), followed by unrelated donors (n = 2,264; 41.2%). Living kidney transplants from relatives comprised a smaller proportion of the total transplants for people with majority monogenic primary kidney disease compared with minority monogenic primary kidney disease and other primary kidney disease (41.6% majority monogenic primary kidney disease vs 73.1% minority monogenic primary kidney disease and 60.5% other primary kidney disease) (Table 1). The mean age of the recipients was 42 years old (± 16.89 SD). The majority of the recipients were male (n= 3,416; 62.1%), and the majority of donors were female (n = 2,825; 57.8%). The total follow-up time was 50,954.67 person years. The median follow-up time was 8.928 (IQR, 8.526) years. Polycystic kidney disease

Table 2. Clinical Characteristics of Living Kidney Transplantation Recipients and Donors by Donor Relatedness

Characteristics	Unrelated (n = 2,264)	Immediate Relative (n = 2,954)	Distant Relative (n = 282)	*P* Value
Primary KD type				<0.001[a]
Majority monogenic	601 (26.5%)	370 (12.5%)	59 (20.9%)	
Minority monogenic	229 (10.1%)	564 (19.1%)	58 (20.6%)	
Other primary KD	1,434 (63.3%)	2,020 (68.4%)	165 (58.5%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Recipient age, y	51.24 ± 12.12	35.76 ± 16.53	32.58 ± 18.46	<0.001[a]
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Recipient sex				0.3
Female	1,434 (63.3%)	1,812 (61.3%)	170 (60.3%)	
Male	830 (36.7%)	1,142 (38.7%)	112 (39.7%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Recipient ethnicity				<0.001[a]
Caucasian	1,882 (83.1%)	2,449 (82.9%)	204 (72.3%)	
Asian	178 (7.9%)	224 (7.6%)	49 (17.4%)	
ATSI	24 (1.1%)	25 (0.8%)	4 (1.4%)	
Maori	57 (2.5%)	81 (2.7%)	6 (2.1%)	
Pacific	46 (2.0%)	88 (3.0%)	12 (4.2%)	
Other	31 (1.4%)	51 (1.7%)	3 (1.1%)	
Missing	46 (2.0%)	36 (1.2%)	2 (0.7%)	
Recipient smoking status				<0.001[a]
Never	1,323 (59.5%)	2,022 (68.4%)	201 (71.2%)	
Former	762 (34.3%)	681 (23.1%)	66 (23.4%)	
Current	138 (6.2%)	210 (7.1%)	10 (3.5%)	
Missing	41 (1.8%)	41 (1.4%)	5 (1.8%)	
Recipient comorbidities				
Lung disease	120 (5.3%)	118 (4.0%)	14 (5.0%)	0.08
Coronary artery disease	332 (14.7%)	192 (6.5%)	15 (5.3%)	<0.001[a]
Peripheral vascular disease	143 (6.3%)	95 (3.2%)	7 (2.5%)	<0.001[a]
Cerebrovascular disease	117 (5.2%)	76 (2.6%)	4 (1.4%)	<0.001[a]
Diabetes mellitus	354 (15.6%)	229 (7.8%)	23 (8.2%)	<0.001[a]
HLA mismatch	4.16 ± 1.39	2.13 ± 1.31	3.21 ± 1.52	<0.001[a]
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Cold ischemia time, h	3.14 ± 2.22	2.66 ± 1.88	2.65 ± 1.51	<0.001[a]
Missing	56 (2.5%)	57 (1.9%)	7 (2.5%)	
Pre-emptive	706 (31.2%)	945 (32.0%)	62 (22.0%)	0.003[b]
Dialysis vintage, mo	17.62 ± 23.63	12.56 ± 19.27	17.14 ± 23.64	<0.001[a]
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Donor age, y	50.50 ± 10.74	47.34 ± 11.62	47.72 ± 12.32	<0.001[a]
Missing	0 (0.0%)	1 (0.0%)	0 (0.0%)	
Donor sex				<0.001[a]
Female	1,286 (56.8%)	1,384 (46.9%)	155 (55.0%)	
Male	825 (36.4%)	1,136 (45.1%)	105 (37.2%)	
Missing	153 (6.8%)	434 (14.7%)	22 (7.8%)	
Donor ethnicity				<0.001[a]
Caucasian	1,685 (74.4%)	1,837 (62.2%)	178 (63.1%)	
Asian	85 (3.7%)	128 (4.3%)	31 (11.0%)	
ATSI	34 (1.5%)	53 (1.8%)	6 (2.1%)	
Maori	28 (1.2%)	48 (1.6%)	4 (1.4%)	
Pacific	14 (0.6%)	21 (0.7%)	1 (0.4%)	
Other	28 (1.2%)	34 (1.2%)	4 (1.4%)	
Missing	390 (17.2%)	833 (28.2%)	58 (20.6%)	
Baseline immunosuppression				
Cyclosporin	894 (39.5%)	1,404 (47.5%)	126 (44.7%)	<0.001[a]
Tacrolimus	1,790 (79.1%)	2,110 (71.4%)	216 (76.6%)	<0.001[a]

(Continued)

Table 2 (Cont'd). Clinical Characteristics of Living Kidney Transplantation Recipients and Donors by Donor Relatedness

Characteristics	Unrelated (n = 2,264)	Immediate Relative (n = 2,954)	Distant Relative (n = 282)	*P* Value
Azathioprine	300 (13.3%)	592 (20.0%)	53 (18.8%)	<0.001[a]
Mycophenolate	1,892 (83.6%)	2,527 (85.5%)	249 (88.3%)	0.04[c]
Sirolimus	184 (8.1%)	312 (10.6%)	35 (12.4%)	0.004[b]
Everolimus	146 (6.4%)	174 (5.9%)	20 (7.1%)	0.6
Prednisolone	2,255 (99.6%)	2,899 (98.1%)	282 (100.0%)	<0.001[a]
Primary KD recurrence	141 (6.2%)	247 (8.4%)	19 (6.7%)	0.01[c]
Graft failure	292 (12.9%)	587 (19.9%)	62 (22.0%)	<0.001[a]
Graft failure cause[d]				0.03[c]
Acute rejection	17 (5.8%)	45 (7.7%)	4 (6.5%)	
BKV nephropathy	8 (2.7%)	15 (2.6%)	2 (3.2%)	
De novo glomerulonephritis	10 (3.4%)	19 (3.2%)	3 (4.8%)	
Primary KD recurrence	14 (4.8%)	53 (9.0%)	2 (3.2%)	
Noncompliance	10 (3.4%)	48 (8.2%)	4 (6.5%)	
Vascular cause	15 (5.1%)	31 (5.3%)	1 (1.6%)	
Chronic nephropathy	184 (63.0%)	334 (56.9%)	42 (67.7%)	
Other	32 (11.0%)	33 (5.6%)	4 (6.5%)	
Missing	2 (0.7%)	9 (1.5%)	0 (0.0%)	
Transplant era				<0.001[a]
1998-2003	303 (13.4%)	705 (23.9%)	50 (17.7%)	
2004-2008	504 (22.3%)	780 (26.4%)	68 (24.1%)	
2009-2013	732 (32.3%)	785 (26.6%)	95 (33.7%)	
2014-2020	725 (32.0%)	684 (23.2%)	69 (24.5%)	

Values for continuous variables given as mean ± SD; for categorical variables as number (percentage). Abbreviations: ATSI, Aboriginal and Torres Strait Islander; BKV, BK virus; HLA, human leukocyte antigen; HR, hazard ratio; KD, kidney disease; NA, not applicable.
[a]Significance level $P < 0.001$.
[b]Significance level $P < 0.01$.
[c]Significance level $P < 0.05$.
[d]Graft failure cause percentages expressed as percentage of people with graft failure instead of total sample size.

contributed to 794 of 1,030 (77.1%) of majority monogenic primary kidney disease cases, and reflux nephropathy contributed to 540 of 851 (63.5%) of minority monogenic primary kidney disease cases (Table S1).

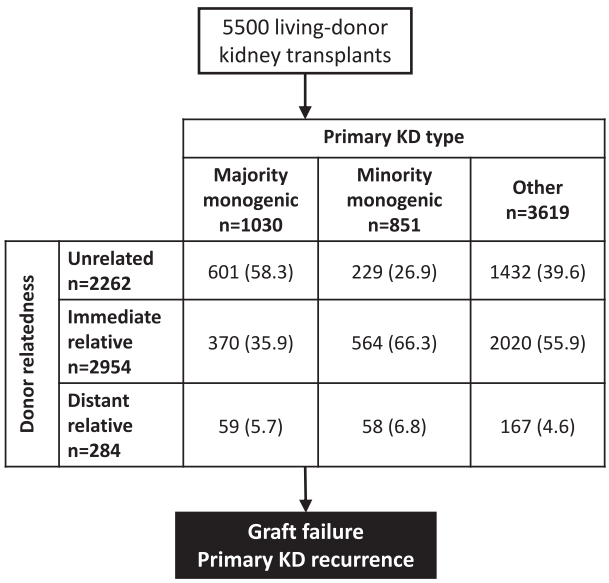

Figure 1. Flowchart of cohorts in study. Abbreviation: KD, kidney disease.

Primary Kidney Disease Recurrence

There were 407 cases (7.4%) of primary kidney disease recurrence (Tables 1 and 2). The primary kidney disease recurrence rate per 1,000 person years was 5.43 for majority monogenic primary kidney disease, 6.32 for minority monogenic primary kidney disease, and 10.07 for other primary kidney disease (Table 3). The primary kidney disease recurrence rate per 1,000 person years was 8.93 for immediate relative, 7.79 for distant relative, and 8.07 for unrelated donors. On univariate analysis, majority monogenic (HR, 0.54 [95% CI, 0.40-0.74], $P < 0.001$) and minority monogenic primary kidney disease (HR, 0.67 [95% CI, 0.50-0.90], $P = 0.01$) were associated with reduced primary kidney disease recurrence compared with other primary kidney disease. On multivariable analyses, these results remained significant (majority monogenic primary kidney disease: AHR, 0.58 [95% CI, 0.42-0.79], $P < 0.001$; minority monogenic primary kidney disease: AHR, 0.64 [95% CI, 0.47-0.87], $P = 0.004$), and a dose-dependent effect was present (Table 3). Grafts from immediate relatives (AHR, 1.25 [95% CI, 1.01-1.54], $P = 0.04$) were associated with increased primary kidney disease recurrence on univariable analyses, but this result

Table 3. Unadjusted and Adjusted Hazard Ratios and 95% Confidence Intervals for the Association Between Primary Kidney Disease Type and Donor Relatedness Characteristics With Primary Kidney Disease Recurrence

Characteristics	Primary KD Recurrence No. (%)	Average Follow-Up Time y ± SD	Primary KD Recurrence Rate per 1,000 Person-Years	Unadjusted HR		Adjusted HR	
				HR (95% CI)	*P* Value	AHR (95% CI)	*P* Value
Primary KD type							
Majority monogenic	49 (12.1%)	8.77 ± 5.17	5.43	0.54 (0.40-0.74)	<0.001[a]	0.58 (0.42-0.79)	<0.001[a]
Minority monogenic	51 (12.5%)	9.49 ± 5.71	6.32	0.67 (0.50-0.90)	0.01[b]	0.64 (0.47-0.87)	0.004[b]
Other primary KD	307 (75.4%)	8.43 ± 5.50	10.07	Reference	Reference	Reference	Reference
Donor relatedness							
Immediate relative	247 (8.4%)	9.37 ± 5.72	8.93	1.25 (1.01-1.54)	0.04[c]	1.11 (0.84-1.47)	0.5
Distant relative	19 (6.7%)	8.60 ± 5.65	8.65	1.04 (0.65-1.69)	0.9	0.90 (0.54-1.50)	0.7
Unrelated	141 (6.2%)	7.73 ± 4.99	8.07	Reference	Reference	Reference	Reference

Abbreviations: AHR, adjusted hazard ratio; HR, hazard ratio; KD, kidney disease.
[a]Significance level $P < 0.001$.
[b]Significance level $P < 0.01$.
[c]Significance level $P < 0.05$.

was not statistically significant in multivariable analyses (AHR, 1.11 [95% CI, 0.84-1.47], P = 0.5). In multivariable analysis, increased recipient age was associated with reduced primary kidney disease recurrence (AHR, 0.91 [95% CI, 0.84-0.98], P = 0.01), and former smoking status was linked to increased primary kidney disease recurrence (Table S3). Partial likelihood ratio test did not reveal any interaction effects between primary kidney disease type and donor relatedness on primary kidney disease recurrence ($\chi^2 = 2.25$, $df = 4$, $P = 0.7$).

Graft Failure

There were 941 cases (17.1%) of graft failure. The graft failure rate per 1,000 person years was 15.1 for majority monogenic primary kidney disease, 24.8 for minority monogenic primary kidney disease, and 21.2 for other primary kidney disease (Table 4). The graft failure rate per 1,000 person years was 22.3 for immediate relative donors, 27.6 for distant relative donors, and 17.1 for unrelated donors. Kaplan-Meier curves showed improved graft survival for majority and minority monogenic primary kidney diseases compared with other primary kidney diseases (Fig 2A). Kaplan-Meier curves showed improved graft survival for immediate relative donor transplants compared with distant relative and nonrelated donor transplants (Fig 2B).

On univariable analyses, majority monogenic (HR, 0.76 [95% CI, 0.66-0.88], P < 0.001) and minority monogenic (HR, 0.84 [95% CI, 0.72-0.97], P = 0.02) primary kidney diseases were associated with reduced graft failure compared with non-monogenic primary kidney diseases (Table 4). Only the signal for reduced graft failure in recipients with majority monogenic primary kidney diseases remained statistically significant after controlling for donor relatedness, recipient age, recipient ethnicity, recipient smoking status, recipient comorbidities, HLA mismatch, dialysis vintage, donor age, and donor ethnicity (AHR, 0.86 [95% CI, 0.74-0.99], P = 0.04; Table 4), although, a dose-dependent effect was observed.

Compared with grafts from unrelated donors, grafts from immediate relatives were associated with reduced graft failure (HR, 0.84 [95% CI, 0.75-0.93], P < 0.001) on univariable analyses, although this was not statistically significant in multivariable analyses. The paradoxical increased graft failure event rate among immediate family donors compared with unrelated donors (22.3 per 1,000 person-years vs 17.1 per 1,000 person-years) was related to the proportionality assumption underpinning both Cox regression and the type of competing risk models we employed, where the relative risk of a clinical end point in one group compared with another remains constant throughout the entire survival experience. Recipient current and former smoking status, coronary artery disease, peripheral vascular disease, diabetes, increasing HLA mismatch, increasing donor age, and non-white donor ethnicity were associated with increased graft failure (Table S4). In the partial likelihood ratio test, there was no

Table 4. Unadjusted and Adjusted Hazard Ratios and 95% CIs for the Association Between Primary Kidney Disease Type and Donor Relatedness With Graft Failure

Characteristics	Graft Failure n (%)	Average Follow-up Time y ± SD	Graft Failure Rate per 1,000 Person-Years	Unadjusted HR		Adjusted HR	
				HR (95% CI)	*P* Value	AHR (95% CI)	*P* Value
Primary KD type							
Majority monogenic	132 (12.8%)	8.48 ± 4.93	15.1	0.76 (0.66-0.88)	<0.001[a]	0.86 (0.74-0.99)	0.04[b]
Minority monogenic	182 (21.4%)	8.64 ± 5.27	24.8	0.84 (0.72-0.97)	0.02[b]	0.97 (0.83-1.13)	0.7
Other primary KD	627 (17.3%)	8.17 ± 5.14	21.2	Reference	Reference	Reference	Reference
Donor relatedness							
Immediate relative	587 (19.9%)	8.90 ± 5.36	22.3	0.84 (0.75-0.93)	<0.001[a]	1.09 (0.94-1.26)	0.3
Distant relative	62 (22.0%)	7.96 ± 5.08	27.6	1.03 (0.82-1.30)	0.8	1.20 (0.94-1.53)	0.2
Unrelated	292 (12.9%)	7.56 ± 4.71	17.1	Reference	Reference	Reference	Reference

Abbreviations: AHR, adjusted hazard ratio; HR, hazard ratio; KD, kidney disease.
[a]Significance level $P < 0.001$.
[b]Significance level $P < 0.05$.

interaction between primary kidney disease types and donor relatedness in graft failure ($\chi^2 = 0.75$, $df = 4$, $P = 0.9$). In competing risk analyses, primary kidney disease type and donor relatedness were not associated with a statistically significant effect on mortality-censored graft failure (Table S5, Fig S1).

Mortality

Donor relatedness and primary kidney disease type were not associated with mortality in the multivariable analysis (Table S6). In the competing risk analysis of graft failure-censored mortality, minority monogenic primary kidney disease was associated with reduced mortality compared with other primary kidney disease (Fig S1, Table S7).

Discussion

This study investigated the effect of primary kidney disease type and donor relatedness on primary kidney disease recurrence, graft failure, and mortality after living donor transplantation. Majority monogenic and minority monogenic were associated with reduced primary kidney disease recurrence risk compared with other primary kidney disease. Furthermore, a dose-dependent effect was observed. Donor relatedness was not associated with primary kidney disease recurrence. There was no interaction between primary kidney disease type and donor relatedness with respect to primary kidney disease recurrence. Majority monogenic primary kidney disease was associated with reduced graft failure compared with other primary kidney disease. There was no correlation between donor relatedness and graft failure. There was no interaction between primary kidney disease type and donor relatedness with respect to graft failure.

The graded reduction in primary kidney disease recurrence risk with primary kidney diseases of decreasing monogenic basis reflects that monogenic primary kidney diseases predominantly involve structural molecular defects that are intrinsic to the kidney.[18] In this cohort, 98.6% of the monogenic primary kidney disease group and 94.1% of the minority monogenic primary kidney diseases group have monogenic kidney disease associated with structural kidney defects, which do not recur after transplantation (Table S1). Furthermore, routine predonation testing prevents the implantation of kidneys from people with genetic defects associated with monogenic kidney diseases, thereby significantly reducing recurrence risks.[9] By contrast, other primary kidney diseases primarily involve extrinsic mechanisms of kidney damage (eg, hyperglycemia in diabetes mellitus and autoimmunity in lupus nephritis), which are not removed with transplantation. The genetic basis of other primary kidney diseases is also predominantly multifactorial (eg, diabetes or lupus nephritis), making primary kidney disease recurrence risk more difficult to identify and quantify during predonation genetic screening.

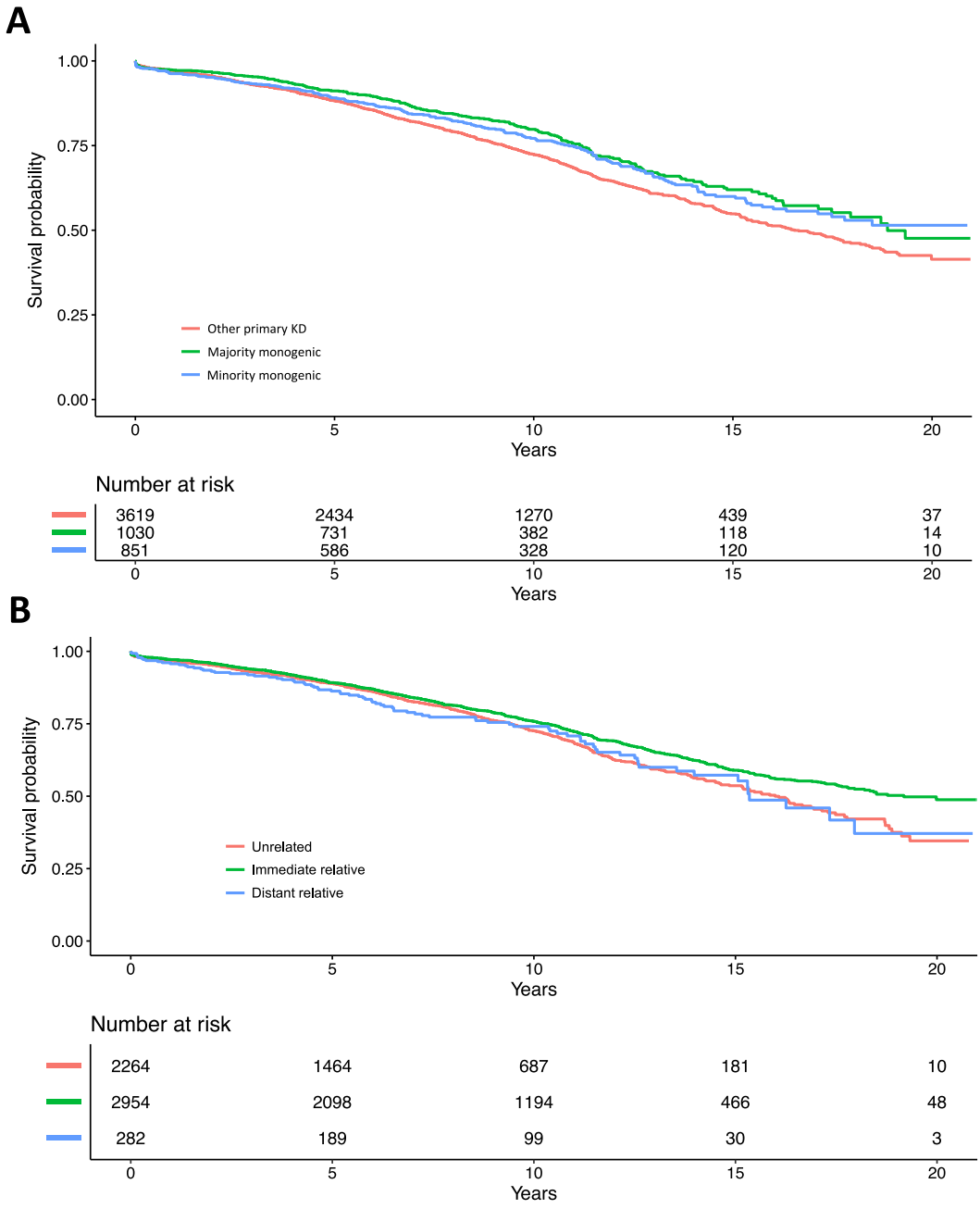

Figure 2. Kaplan-Meier curves and risk tables for graft failure as a function of (A) primary kidney disease type and (B) donor relatedness. Time after transplant presented in years. Abbreviation: KD, kidney disease.

Donor relatedness was not correlated with primary kidney disease recurrence, suggesting that the current predonation screening is adequate to minimize the risk of primary kidney disease transmission in living related transplants. Studies in people with glomerulonephritides have associated living related kidney transplants with an increased risk of disease recurrence.[19–21] Notably, our analysis included all types of primary kidney disease. As such, any potential correlations between donor relatedness and primary kidney disease recurrence for rare diseases with heritable components such as glomerulonephritides may be outweighed by large numbers of primary kidney diseases with no relationship between donor relatedness and primary kidney disease recurrence (eg, lead nephropathy or lithium toxicity).

The absence of interaction between primary kidney disease type and donor relatedness demonstrates that unmeasurable genetic factors shared between related donor-recipient pairs do not alter primary kidney disease recurrence, regardless of the monogenic basis of primary kidney disease. This finding is particularly significant in the context of non-monogenic primary kidney diseases where

there is no method to quantify primary kidney disease risks despite growing evidence of familial clustering of nephropathy[6-8] and heritability of kidney function.[22-24] Current live donor selection practices in Australia and New Zealand are adequate to navigate the primary kidney disease recurrence risk associated with donor relatedness, with 53.7% transplants between zero- and first-degree relatives.

Majority monogenic primary kidney diseases were linked to reduced graft failure compared with other primary kidney disease, which is consistent with findings from people with Fabry disease, polycystic kidney disease, cystinosis, and Alport's disease.[25-28] This finding may reflect that patients with majority monogenic primary kidney diseases have reduced infection, cancer, and metabolic syndrome risk. As a result, people with monogenic primary kidney diseases are able to tolerate higher levels of immunosuppression, leading to reduced acute rejection and chronic allograft nephropathy (Table 1). This is consistent with US transplant registry studies showing that death-censored graft failure was higher among older patients who received antimetabolite avoidance, mammalian target of rapamycin (mTOR) inhibitor-based, and cyclosporine-based regimens.[29] Further studies are required to test this hypothesis.

Donor relatedness was not associated with graft failure after adjusting for recipient age, recipient ethnicity, recipient smoking status, recipient comorbidities, HLA mismatch, dialysis vintage, donor age, and donor ethnicity. This is consistent with unadjusted findings from the United Network for Organ Sharing (UNOS) Renal Transplant Registry and Organ Procurement and Transplantation Network where there was no survival difference between unrelated and related live donor grafts.[5,14] Husain et al[5] also identified that after adjustment for HLA mismatches, donor and recipient characteristics, and transplant era, donor relatedness was associated with higher death-censored graft failure, especially in the context of transplants from African American donors or excluding monogenic cystic disease. Differences in local genetic and/or socioenvironmental factors may also contribute to the conflicting findings between Husain et al[5] and our study, underscoring the need to investigate kidney transplantation outcomes in each locality.

No interaction was observed between primary kidney disease type and donor relatedness with respect to graft failure. This result suggests that unmeasurable genetic factors did not impact significantly on graft failure risk. Notably, living related donor kidneys tended were associated with reduced donor age, recipient comorbidities, and dialysis vintage—all of which were associated with superior graft failure rates. It is possible that these factors may overshadow small interactions between primary kidney disease type and donor relatedness.

In this study, primary kidney disease was classified based on current knowledge regarding the monogenic basis of kidney disease. It is possible that monogenic diseases may be present in the other primary kidney disease group—this is particularly true in the context of glomerulonephritides, which demonstrates strong familial clustering. Potential misclassification of other primary kidney diseases may impact the delineation between the primary kidney disease type categories thereby, reducing the power and sensitivity of the analyses to reject the null hypothesis. Notably, majority monogenic primary kidney disease primarily comprises conditions known to have a monogenic basis, such as polycystic kidney diseases and familial glomerulonephritis, while minority monogenic primary kidney disease includes conditions with reduced monogenic basis. This graded categorization of primary kidney disease enabled the observation of a "dose effect" for primary kidney disease recurrence, strengthening our confidence in the results.

Polycystic kidney disease comprised 77.1% of the recipients in the majority monogenic primary kidney disease group, and reflux nephropathy comprised 63.5% of the minority monogenic group. It is unlikely this overweighting would bias the recurrence results because the other primary kidney diseases included in each of these groups demonstrate similar recurrence patterns (eg, polycystic kidney disease and medullary cystic disease in the majority monogenic group).

Primary kidney disease recurrence was defined by the identification of primary kidney disease recurrence on for-cause biopsies and/or primary kidney disease recurrence being listed as a cause for graft failure. This approach allowed the inclusion of cases where a primary kidney disease recurrence diagnosis was not histologically pursued (eg, diabetic nephropathy, immunoglobulin A nephropathy). However, primary kidney disease recurrence episodes that were not biopsy-confirmed in a functioning graft would not be captured in this analysis because suspected cases of primary kidney disease recurrence (without biopsy confirmation) are not recorded in ANZDATA. Further studies with protocol biopsies for all suspected primary kidney disease recurrence cases would be required to measure the true primary kidney disease recurrence rate to determine the impact of ascertainment bias. Such a study would be difficult to justify ethically because it exposes patients to the risks of a kidney biopsy, the results of which are unlikely to change their disease management.

Primary kidney disease recurrence affected 7.4% and graft failure affected 17.1% of participants. Due to the small number of events, the absence of an interaction between primary kidney disease type and donor relatedness will require confirmation in a larger cohort. Finally, our study was a retrospective observational study (registry analysis) with limitations associated with unmeasured confounders.

The major strength of this study is the use of a binational kidney failure registry to investigate the effect of primary kidney disease type and donor relatedness in the modern era. Majority monogenic and minority monogenic primary kidney diseases were associated with reduced

primary kidney disease recurrence compared with other primary kidney disease. Majority monogenic primary kidney disease was associated with reduced graft failure compared with other primary kidney disease. Donor relatedness was not associated with primary kidney disease recurrence nor with graft failure. There was no interaction between primary kidney disease type and donor relatedness in primary kidney disease recurrence or graft failure. Our findings inform the clinical care and prognostication of live donor kidney transplant recipients in terms of potential recipient and graft outcomes. This includes illuminating clinical scenarios for heightened focus on non-monogenic primary kidney diseases and managing underlying comorbidities. These findings are important for counseling with regard to outcomes after live donor kidney transplantation for potential recipients in the context of their individualized primary kidney disease and donor source.

Supplementary Material

Supplementary File (PDF)

Figure S1: Competing risk analyses of graft failure-censored mortality and mortality-censored graft failure as a function of primary kidney disease type versus time, and donor relatedness versus time.

Table S1: Breakdown of sample size for primary renal disease heritability classification by primary renal disease type.

Table S2: Classification of donor relatedness.

Table S3: Unadjusted and adjusted HRs and 95% CIs for the association between donor and recipient characteristics with primary kidney disease recurrence.

Table S4: Unadjusted and adjusted HRs and 95% CIs for the association between donor and recipient characteristics with graft failure.

Table S5: Completing risk analysis of mortality-censored graft failure in Fine and Gray subdistribution model.

Table S6: Unadjusted and adjusted HRs and 95% CIs for the association between donor and recipient characteristics with mortality.

Table S7: Completing risk analysis of graft failure-censored mortality in Fine and Gray subdistribution model.

Article Information

Authors' Full Names and Academic Degrees: Dong Yu, MD, Eva Malacova, PhD, Cameron Hurst, PhD, Monica Suet Ying Ng, PhD, and Andrew John Mallett, PhD.

Authors' Affiliations: Faculty of Medicine (DY, AJM) and School of Public Health (CH), University of Queensland, QIMR Berghofer Medical Research Institute (EM, CH), Kidney Health Service, Royal Brisbane and Women's Hospital (MSYN), and Conjoint Internal Medicine Laboratory, Chemical Pathology, Pathology Queensland, Health Support Queensland (MSYN), Herston; Nephrology Department (MSYN), Princess Alexandra Hospital (DY), Woolloongabba; Faculty of Health, Queensland University of Technology (EM), Molly Wardaguga Research Centre, Charles Darwin University (CH), and Institute for Molecular Biosciences, University of Queensland (MSYN, AJM), Brisbane; and Department of Renal Medicine, Townsville University Hospital (AJM), and College of Medicine and Dentistry, James Cook University (AJM), Townsville, Australia.

Address for Correspondence: Monica Suet Ying Ng, PhD, Kidney Health Service, Royal Brisbane and Women's Hospital, Herston, QLD, 4029, Australia. Email: monica.ng@health.qld.gov.au or Andrew John Mallett, PhD, Department of Renal Medicine, Townsville University Hospital, Douglas, QLD, 4029, Australia. Email: andrew.mallett@health.qld.gov.au

Authors' Contributions: Research idea and study design: MSYN, EM, CH, AJM; data acquisition: DY, MSYN, AJM; data management/processing: EM, CH, MSYN; statistical analyses: EM, CH; mentorship: MSYN, AJM. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: Dr Ng is supported by the Robert and Janelle Bird Postdoctoral Research Fellowship 2020. Dr Mallett is supported by a Queensland Health Advancing Clinical Research Fellowship. The funders did not have any role in study design, data collection, analysis, reporting, or decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The authors are grateful for the significant contributions of the Australian and New Zealand kidney medicine community (physicians, surgeons, database managers, nurses, and patients) in providing information for and maintaining the ANZDATA Registry.

Disclaimer: The analyses and interpretation presented are those of the authors, not ANZDATA.

Peer Review: Received July 21, 2022. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form April 21, 2023.

References

1. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. *Nat Rev Nephrol*. 2020;16(10):573-585. doi:10.1038/s41581-020-0315-4
2. Chapman JR, Kanellis J. Kidney donation and transplantation in Australia: more than a supply and demand equation. *Med J Aust*. 2018;209(6):242-243. doi:10.5694/mja18.00617
3. Naderi GH, Mehraban D, Kazemeyni SM, Darvishi M, Latif AH. Living or deceased donor kidney transplantation: a comparison of results and survival rates among Iranian patients. *Transplant Proc*. 2009;41(7):2772-2774. doi:10.1016/j.transproceed.2009.07.041
4. Matas AJ, Payne WD, Sutherland DE, et al. 2,500 living donor kidney transplants: a single-center experience. *Ann Surg*. 2001;234(2):149-164. doi:10.1097/00000658-200108000-00004
5. Husain SA, King KL, Sanichar N, Crew RJ, Schold JD, Mohan S. Association between donor-recipient biological relationship and allograft outcomes after living donor kidney transplant. *JAMA Netw Open*. 2021;4(4):e215718. doi:10.1001/jamanetworkopen.2021.5718
6. Skrunes R, Svarstad E, Reisæter AV, Vikse BE. Familial clustering of ESRD in the Norwegian population. *Clin J Am Soc Nephrol*. 2014;9(10):1692-1700. doi:10.2215/cjn.01680214
7. Connaughton DM, Bukhari S, Conlon P, et al. The Irish Kidney Gene Project—prevalence of family history in patients with

kidney disease in Ireland. *Nephron*. 2015;130(4):293-301. doi:10.1159/000436983
8. McClellan WM, Satko SG, Gladstone E, Krisher JO, Narva AS, Freedman BI. Individuals with a family history of ESRD are a high-risk population for CKD: implications for targeted surveillance and intervention activities. *Am J Kidney Dis*. 2009;53(3)(suppl 3):S100-S106. doi:10.1053/j.ajkd.2008.07.059
9. Caliskan Y, Lee B, Whelan A, Abualrub F, Lentine KL, Jittirat A. Evaluation of genetic kidney diseases in living donor kidney transplantation: towards precision genomic medicine in donor risk assessment. *Curr Transplant Rep*. 2022;9(2):127-142. doi:10.1007/s40472-021-00340-3
10. Mier MG, Lara-Gutierrez J, Garcia-Esquina J, et al. Kidney transplantation from spousal donors have excellent patient/graft outcomes similar to living related kidney transplantation: 10-year single Mexican center experience. *Transplantation*. 2014;98(suppl 1):257. World Transplant Congress 2014 abstract C1632. https://journals.lww.com/transplantjournal/toc/2014/07151
11. Ishikawa N, Yagisawa T, Sakuma Y, et al. Kidney transplantation of living unrelated donor-recipient combinations. *Transplant Proc*. 2012;44(1):254-256. doi:10.1016/j.transproceed.2011.11.019
12. Roozbeh J, Mehdizadeh AR, Izadfar MA, Razmkon A, Salahi H, Malek-Hosseini SA. Comparison of spousal with other donor groups: study of a single center. *Transplant Proc*. 2006;38(2):562-563. doi:10.1016/j.transproceed.2005.12.058
13. Ozgen U, Ozban M, Birsen O, et al. Spousal and living related kidney transplantation: our center experience. *BMC Surg*. 2021;21(1):444. doi:10.1186/s12893-021-01447-1
14. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med*. 1995/08/10 1995;333(6):333-336. doi:10.1056/NEJM199508103330601
15. Tang S, Lui SL, Lo CY, et al. Spousal renal donor transplantation in Chinese subjects: a 10 year experience from a single centre. *Nephrol Dial Transplant*. 2004;19(1):203-206. doi:10.1093/ndt/gfg492
16. D'Alessandro AM, Sollinger HW, Knechtle SJ, et al. Living related and unrelated donors for kidney transplantation a 28-year experience. *Ann Surg*. 1995;222(3):353-364. doi:10.1097/00000658-199509000-00012
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
18. Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. *Kidney Int*. 2020;98(3):590-600. doi:10.1016/j.kint.2020.03.031
19. Brensilver JM, Mallat S, Scholes J, McCabe R. Recurrent IgA nephropathy in living-related donor transplantation: recurrence or transmission of familial disease? *Am J Kidney Dis*. 1988;12(2):147-151. doi:10.1016/s0272-6386(88)80010-6
20. Kennard AL, Jiang SH, Walters GD. Increased glomerulonephritis recurrence after living related donation. *BMC Nephrol*. 2017;18(1):25. doi:10.1186/s12882-016-0435-z
21. Seshan SV, Salvatore SP. Recurrent glomerular diseases in renal transplantation with focus on role of electron microscopy. *Glomerular Dis*. 2021;1(4):205-236. doi:10.1159/000517259
22. Fox CS, Yang Q, Cupples LA, et al. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. *J Am Soc Nephrol*. 2004;15(9):2457-2461. doi:10.1097/01.asn.0000135972.13396.6f
23. Gorski M, van der Most PJ, Teumer A, et al. 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function. *Sci Rep*. 2017;7:45040. doi:10.1038/srep45040
24. Zanetti D, Rao A, Gustafsson S, Assimes TL, Montgomery SB, Ingelsson E. Identification of 22 novel loci associated with urinary biomarkers of albumin, sodium, and potassium excretion. *Kidney Int*. 2019;95(5):1197-1208. doi:10.1016/j.kint.2018.12.017
25. Ng MS, Malacova E, Hurst C, Johnson DW, Mallett AJ. Clinical outcomes of people with fabry disease—ANZDATA Registry Study. *Kidney Int Rep*. 2021;6(9):2481-2485. doi:10.1016/j.ekir.2021.06.013
26. Bhutani G, Astor BC, Mandelbrot DA, et al. Long-term outcomes and prognostic factors in kidney transplant recipients with polycystic kidney disease. *Kidney360*. 2021;2(2):312. doi:10.34067/KID.0001182019
27. Cohen C, Charbit M, Chadefaux-Vekemans B, et al. Excellent long-term outcome of renal transplantation in cystinosis patients. *Orphanet J Rare Dis*. 2015;10(1):90. doi:10.1186/s13023-015-0307-9
28. Kelly YP, Patil A, Wallis L, et al. Outcomes of kidney transplantation in Alport syndrome compared with other forms of renal disease. *Ren Fail*. 2017;39(1):290-293. doi:10.1080/0886022x.2016.1262266
29. Cheungpasitporn W, Lentine KL, Tan JC, et al. Immunosuppression considerations for older kidney transplant recipients. *Curr Transplant Rep*. 2021;8(2):100-110. doi:10.1007/s40472-021-00321-6

Association of Primary Kidney Disease Type and Donor-Relatedness With Live Donor Kidney Transplant Outcomes

Setting & Participants

ANZDATA registry analysis

Retrospective observational study

N = 5,500 living donor kidney transplants

1998-2018

Exposures

Primary kidney disease (KD)

- Majority monogenic
- Minority monogenic
- Other primary KD

Donor relatedness

- **Immediate relative:** 0° and 1° relatives
- **Distant relative:** 2° and 3° relatives
- **Unrelated**: genetically unrelated

Results

Compared With Other Primary KD

Adjusted HR (95%CI)

Primary KD Type	Primary KD Recurrence	Graft Failure
Majority Monogenic	**0.58** (0.42-0.79) *P*<0.001	**0.86** (0.74-0.99) *P*=0.04
Minority Monogenic	**0.64** (0.47-0.87) *P*=0.004	0.97 (0.83-1.13) *P*=0.7

- **No association between donor relatedness and graft outcomes**
- **No interaction between primary KD type and donor relatedness**

CONCLUSION: Monogenic primary KD is associated with lower rates of primary KD recurrence and allograft failure. Donor relatedness was not associated with allograft outcomes.

Dong Yu, Eva Malacova, Cameron Hurst, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2023.04.004