ORIGINAL ARTICLE

Patient and center characteristics associated with kidney transplant outcomes: a binational registry analysis

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SUMMARY

This registry-based study evaluated the contribution of center characteristics to kidney transplant outcomes in adult first kidney transplant recipients in Australia and New Zealand between 2004 and 2014. Primary outcomes were mortality and graft failure, and secondary outcomes were transplant complications. Overall, 6970 transplants from 17 centers were included. For deceased donor transplants, 5-year patient and graft survival rates varied considerably (81.0–93.9% and 72.2–88.3%, respectively). Variations in mortality and graft failure were partially reduced after adjustment for patient characteristics (1% and 20% reductions) and more markedly reduced after adjustment for center characteristics (41% and 55% reductions). For living donor transplants, 5-year patient and graft survival rates varied (89.7–100% and 79.2–96.9%, respectively). Centers with high average total ischemic times (>14 h) were associated with higher mortality for both deceased (adjusted hazard ratio [(AHR] 2.24, 95% CI 1.21–4.13) and living donor transplants (AHR 1.76, 95% CI 1.02–3.04). Small center size (<35 new kidney transplants/year) was associated with a lower hazard of mortality for living donor kidney transplants (AHR 0.48, 95% CI 0.28–0.81). No center characteristic was associated with graft failure. The appreciable variations in deceased donor kidney transplant recipient and graft survival outcomes across centers were attributable to center effects.

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Key words
center characteristics, center effects, center variation, graft survival, kidney transplant, patient survival

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Introduction

The incidence of end-stage kidney disease (ESKD) is increasing worldwide [1–3]. Kidney transplantation is widely recognized as the optimal modality of kidney replacement therapy for most patients with ESKD because it generally results in superior survival and quality of life compared with dialysis [4–6]. Given the widespread shortage of organs available for kidney transplantation [7], it is critically important to identify modifiable factors associated with the attainment of better kidney transplant outcomes, such as patient and graft survival. Transplant outcomes have been shown to be associated with both donor characteristics (such as age and type) and recipient characteristics (such as age, human leukocyte antigen [HLA] mismatch, sensitization status, ESKD duration, diabetes and presence of cardiovascular disease) [8]. Apart from these patient characteristics, center effects related to center practices, experience, or organization may also play an important role in influencing kidney transplant outcomes, given that appreciable variations in patient survival and/or graft survival have been reported across centers in the USA, Canada, and United Kingdom [9–13]. However, the findings of these studies suffer from a number of limitations including the use of outdated cohorts (prior to 2000), the failure to analyze living and deceased donor kidney transplants separately, and the evaluation of only one or a very limited number of center characteristics (typically center size) [11]. Moreover, the relative contributions of patient and center factors to kidney transplant outcomes have not been robustly or comprehensively studied.

The aim of this retrospective, observational cohort study was to evaluate the association of patient and center factors with kidney transplant outcomes in a contemporary cohort (2004–2014) of first kidney transplant recipients in Australia and New Zealand using data obtained from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. Living and deceased donor kidney transplant recipients were analyzed separately.

Materials and methods

The study included all adult recipients (≥18 years) of first kidney transplants performed in Australia and New Zealand between January 2004 and December 2014 [14].The study only included ABO compatible kidney transplants. ABO-incompatible transplants were excluded from the study. The use of de-identified ANZDATA Registry data for the study was approved by the Princess Alexandra Hospital Human Research Ethics Committee. Permission to use ANZDATA data was granted by the ANZDATA Registry executive.

Data collection

Patient-level data collected included age, gender, ethnicity (five groups: Caucasian, Asian, Aboriginal and Torres Strait Islander[ATSI], Maori and Pacific Islander [MP], and others), body mass index(BMI), smoking status (three groups: non-smokers, current smokers, and former smokers), comorbid conditions including the presence of cardiovascular disease (a composite of ischemic heart disease, cerebrovascular disease and peripheral vascular disease), diabetes mellitus, chronic lung disease, primary cause of ESKD (five groups: glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, polycystic kidney disease, and other causes), late referral (defined as initiation of dialysis <3 months after referral to a nephrology service), last modality of kidney replacement therapy (KRT) before transplant (classified as hemodialysis[HD], peritoneal dialysis [PD], or pre-emptive transplant). Other data collected included total ischemic time, number of HLA mismatches at the -A -B and -DR loci (3 groups: 0–1, 2–4, and 5–6), and percentage of peak panel reactive antibody (PRA) (4 groups: 0%, 1–<20%, 20–<50%, and ≥ 50%). In addition, donor characteristics for deceased donor kidney transplant were included using Australian kidney donor risk index (KDRI) scores using the formula developed by Rao et al.[15]

The transplant center was defined as the center where transplant surgery occurred. Center-level characteristics included center size (defined as the average number of incident transplant patients in a center per year), percentage of patients who were transplanted and followed up in the same center, and average ischemic time for deceased donor transplants in a center. Center characteristics were first divided into quartiles, and then, the second and third quartiles were combined as a middle group which served as the reference group in regression analyses[16,17].

Outcomes of study

The primary outcomes were all-cause mortality and graft failure. Graft failure was defined as failure to sustain adequate renal function and requiring kidney replacement therapy (dialysis or re-transplantation) or death with a functioning graft. The secondary outcomes were death-censored graft failure, delayed graft function

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(DGF; defined in the ANZDATA registry as the lack of a spontaneous (>10%) fall in serum creatinine and dialysis required within 72 h), acute rejection (defined as any form of biopsy-proven acute rejection including cellular, humoral, or combination), and death with functioning graft.

Statistical analysis

Baseline characteristic data were presented as frequency (percentage) for categorical variables and mean ± standard deviation for normally distributed continuous variables. The primary outcomes, all-cause-mortality and graft failure, were analyzed using multilevel parametric survival models to account for patients clustered within the same center. The Weibull survival distribution model was selected based on the lowest Akaike information criterion (AIC). All patient and center characteristics were included as covariates in the primary outcome analyses. Interactions were tested for biologically plausible effect modification by introducing a first-order multiplicative interaction term.

The same covariates were used for all the secondary outcomes analyses. All secondary outcomes, except death-censored graft failure, were analyzed using multivariable logistic regression. Death-censored graft failure was analyzed using parametric survival models. All primary and secondary outcomes were analyzed separately for living donor and deceased donor transplants. Bonferroni correction was performed for the multiple outcomes studied. Percentage reductions in variations in hazards of death and graft failure for living and deceased donor transplants across centers due to patient characteristics were calculated as the ratios of the differences in the standard deviations (SD) of center hazards from an unadjusted model and a patient characteristics model relative to the standard deviation of center hazards for the unadjusted model $[(SD_{unadjusted} - SD_{patient})/SD_{unadjusted}] \times 100$. Percentage reductions in variations in hazards of death and graft failure for living and deceased donor transplants across centers due to center characteristics were calculated similarly relative to the patient-level characteristics model, $[(SD_{patient} - SD_{center})/ SDpatient] \times 100$ [16,17]. Data were analyzed using Stata version 14.0 (StataCorp LP). *P*-values <0.05 were considered statistically significant.

Results

A total of 8779 ABO compatible kidney transplants were performed during the study period. Of these, 7715 were first kidney transplants. After excluding patients with missing data ($n = 662$; 9%) and patients from a center with less than 10 transplants per year ($n = 77$), 6970 transplants performed at 17 transplanting centers remained, comprising 2721(39%) living donor transplants and 4249 (61%) deceased donor transplants (Fig. 1). Characteristics of the study participants by donor type are presented in Table 1.

Deceased donor kidney transplant

Death (all-cause)

A total of 479 (11%) patients died during the study period (Table S1). The median follow-up period for deceased donor transplant patients was 4.10 years (IQR: 2.04–6.77 years). The center 5-year patient survival for deceased donor kidney transplants varied 1.16-fold from 81.0% to 93.9% across the 17 centers (Fig. S1). Variation in the hazards of mortality across centers was reduced by 1% after adjusting for patient-level characteristics and by an additional 41% after adjusting for center-level characteristics (Fig. 2; Table S2). Centers characteristic significantly associated with mortality was average total ischemic time for deceased donor kidney transplant of a center with average total ischemic times of >14 h were significantly associated with a higher hazard of mortality compared with centers with average total ischemic times of <12 h (HR 2.24, 95% CI 1.21–4.13) (data not shown). Patient characteristics associated with mortality were older age, Indigenous race (ATSI), current smoking, cause of ESKD attributed to diabetic nephropathy or other causes, presence of cardiovascular disease, longer time on dialysis, and higher PRA values (>50%; Table 2). The donor characteristics associated with mortality was higher KDRI score. The mean KDRI scores for the entire cohort and small, medium, and large centers were 1.36, 1.41, 1.38, and 1.25, respectively. There was no interaction between KDRI score and center size in multilevel parametric survival analysis.

Graft failure

A total of 791 (19%) patients experienced graft failure during the study period (Table S1). The center 5-year graft survival varied 1.22-fold from 72.2% to 88.3% across 17 centers (Fig. S2). Variation in the hazards of graft failure across centers was reduced by 20% after adjusting for patient-level characteristics and by an additional 55% after adjusting for center-level

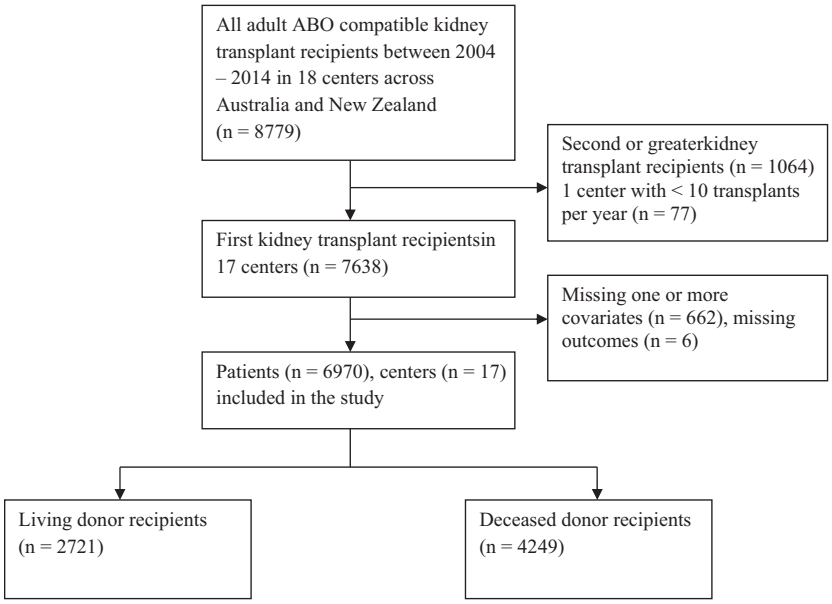

Figure 1 Study cohorts.

characteristics (Fig. 3). There were no specific center characteristics associated with graft failure. Patient characteristics associated with graft failure were Indigenous race (ATSI), current smoking, former smoking, presence of cardiovascular disease, longer time on dialysis, and higher PRA percentage (≥20%; Table 3). The donor characteristic associated with graft failure was higher KDRI score.

Further exploratory analyses (by adding one center characteristic at a time in analyses) suggested that the main center characteristic contributing to variation in deceased donor graft and patient survival was the proportion of patients transplanted and followed up in the same center.

Death-censored graft failure

A total of 423 (10%) patients experienced death-censored graft failure during the study period (Table S1). The center 5-year death-censored graft survival varied 1.16-fold from 81.0% to 93.8% across 17 centers. Variation in the hazards of death-censored graft failure across centers was increased by 15% after adjusting for patient-level characteristics, but reduced by 28% after adjusting for center-level characteristics. No specific center characteristics were associated with death-censored graft failure. Patient characteristics significantly associated with higher death-censored graft failure were younger patient age, ATSI and Maori and Pacific Islander (MP) race, current and former smoking, and higher PRA percentage, and the donor characteristic associated with death-censored graft failure was higher KDRI score (Table S3).

Delayed graft function

A total of 1208 (28%) patients experienced delayed graft function during the study period (Table S1). The center delayed graft function (DGF) varied 3.25-fold from 13.8% to 44.9% across 17 Australian and New Zealand centers. Variation in the odds of DGF across centers was reduced by 2% after adjusting for patient-level characteristics and by an additional 28% after adjusting for center-level characteristics. However, there were no specific center characteristics found to be associated with DGF. The patient characteristics associated with DGF included male gender, higher BMI, prior HD, longer dialysis duration, and higher HLA mismatch, and the donor characteristic associated with DGF was higher KDRI score (Table S4).

Acute rejection

A total of 1028 (24%) patients developed acute rejection during the study period (Table S1). The center acute rejection rate varied 5.43-fold from 7.3% to 39.5% across 17 centers. Variation in the odds of acute rejection across centers was increased by 13% after adjusting for patient-level characteristics but reduced by 16% after adjusting for center-level characteristics. However, no specific center characteristic was independently associated with acute rejection. The patient characteristics

Table 1. Patient- and center-level characteristics.

Variables	All patients (n = 6970)	Living donor recipients (n = 2721)	Deceased donor recipients (n = 4249)
Patient characteristics			
Age (years)	49.2 ± 13.0	45.8 ± 14	51.3 ± 12
Gender (male)	4434 (64)	1742 (64)	2697 (64)
Race			
Caucasian	5502 (79)	2301 (85)	3205 (75)
Asian	786 (11)	249 (9.2)	538 (12.5)
ATSI	223 (3)	21 (0.8)	202 (5)
MP	353 (5)	120 (4)	233 (5.5)
Other	106 (2)	30 (1)	77 (2)
Body mass index(kg/m^2)	26.6 ± 5.3	26.2 ± 4.8	26.9 ± 5.5
Smoking status			
Non-smoker	3886 (56)	1685 (62)	2201 (52)
Current smoker	747 (11)	187 (7)	560 (13)
Former smoker	2337 (33)	849 (31)	1488 (35)
Primary renal disease			
Glomerulonephritis	3134 (45)	1271 (47)	1863 (44)
Diabetic nephropathy	787 (11.5)	210 (8)	577 (14)
Hypertensive nephropathy	445 (6.5)	138 (5)	307 (7)
Polycystic kidney disease	1127 (16)	473 (17)	654 (15)
Other	1477 (21)	629 (23)	848 (20)
Diabetes mellitus	1492 (21)	426 (16)	1066 (25)
Cardiovascular disease	1806 (26)	494 (18)	1312 (31)
Chronic lung disease	576 (8)	157 (6)	419 (10)
Late referral to nephrologist	1190 (17)	366 (14)	824 (19)
Last modality of KRT			
Hemodialysis	4282 (62)	1323 (49)	2959 (70)
Peritoneal dialysis	1830 (26)	571 (21)	1259 (30)
Kidney transplant (pre-emptive)	858 (12)	827 (30)	31 (1)
Dialysis vintage (years)	3.0 ± 2.7	1.3 ± 1.8	4.0 ± 2.7
PRA class			
0%	3380 (48)	1486 (55)	1894 (44.5)
1–<20%	2617 (38)	932 (34)	1685 (40)
20–<50%	510 (7)	182 (7)	328 (7.5)
≥50%	463 (7)	121 (4)	342 (8)
Number of HLA mismatches			
0–1	889 (13)	359 (13)	530 (12)
2–4	3838 (55)	1637 (60)	2201 (52)
5–6	2243 (32)	725 (27)	1518 (36)
Total ischemic time (hours)	8.8 ± 6.0	2.9 ± 1.9	12.5 ± 4.5
KDRI			1.27 (1.0 −1.64)
Center characteristics (n = 17)			
Center size (number of incident transplants per year)	34.0 (27.8–72.2)		
Average total ischemic time for deceased donor transplant (hours)	12.6 (11.5–13.6)		
% patients transplanted and followed up in the same center	63.0 (51.8–72.6)		

Data are presented as frequency (%), mean ± standard deviation or median (interquartile range).

ATSI, Aboriginal and Torres Strait Islander; HLA, human leukocyte antigen; MP, Maori and Pacific Islanders; PRA, panel reactive antibody; KRT, kidney replacement therapy; KDRI, Kidney Donor Risk Index.

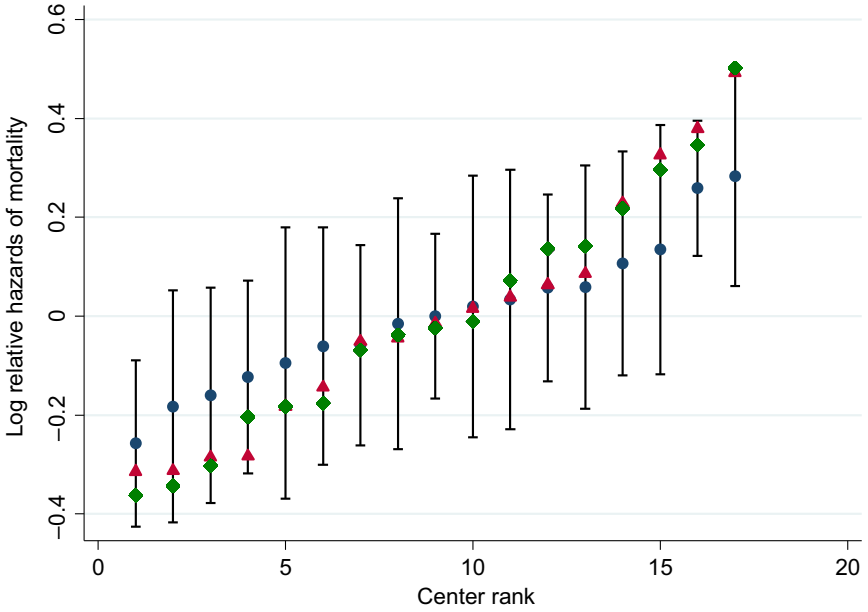

Figure 2 Log relative hazards of mortality for deceased donor kidney transplant across 17 centers, unadjusted (diamonds), adjusted for patient-level characteristics (triangles), and adjusted for patient- and center-level characteristics (circles). Estimates are shown with 95% confidence intervals for patient- and center-level characteristics adjusted model. The transplant centers are ranked by the log relative hazards of mortality.

associated with acute rejection were younger age, higher BMI, longer time on dialysis, higher PRA, and higher number of HLA mismatches, and the donor characteristic associated with acute rejection was higher KDRI score (Table S4).

Death with functioning graft

A total of 368 (9%) patients died with functioning graft during the study period (Table S1). The center death with functioning graft rate varied 4.42-fold from 4.6% to 20.3% across 17 centers in Australia and New Zealand. Variation in the odds of death with functioning graft across centers was increased by 15% after adjusting for patient-level characteristics, but reduced by 28% after adjusting for center-level characteristics. No specific center characteristic was associated with the odds of death with functioning graft. Patient characteristics associated with death with functioning graft were older age, current smoking, presence of cardiovascular disease, and higher PRA (Table S4).

Living donor kidney transplant

Death (all-cause)

A total of 182 (7%) patients died during the study period (Table S1). The median follow-up period for patients of living donor transplants was 5.60 years (interquartile range (IQR) 3.39–7.84 years). The center 5-year patient survival varied 1.11-fold from 89.7% to 100% across the 17 centers (Fig. S3). Variation in the hazards of mortality across centers was reduced by 32% after adjusting for patient-level characteristics, whereas there was no additional reduction in variation after adjusting for center-level characteristics. Centers with average total ischemic times of <12 h for deceased donor transplants were significantly associated with a lower hazard of mortality (HR 0.53, 95% CI 0.33–0.87) whereas centers with average total ischemic times of >14 h for deceased donor transplant were significantly associated with a higher hazard of mortality (HR 1.76, 95% CI 1.02–3.04) compared with centers with ischemic times of 12–14 h. Small centers (<35 transplants per year) were significantly associated with a lower hazard of mortality (HR 0.48, 95% CI 0.28–0.81) compared with average-sized centers (35–104 transplants per year). Patient characteristics significantly associated with mortality were older age, Indigenous race (ATSI), former smokers, cause of ESKD attributed to diabetic nephropathy or other causes, presence of cardiovascular disease, presence of diabetes mellitus, and higher PRA values (>50%; Table 2).

Graft failure

A total of 370 (14%) patients experienced graft failure during the study period (Table S1). The center 5-year graft survival varied 1.22-fold from 79.2 to 96.9% across

centers (Fig. S4). There was no alteration to the variation in the hazards of graft failure across centers after adjusting for patient- or center-level characteristics. No specific center characteristic was associated with graft failure. Patient characteristics significantly associated with graft failure were Indigenous race (ATSI), former smoking, presence of cardiovascular disease, late nephrologist referral, and higher PRA percentage

Table 2. Multilevel parametric survival model for living and deceased donor kidney transplant patient death.

	Living donor transplant			Deceased donor transplant		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (decade)	1.59	1.37–1.82	<0.001	1.53	1.39–1.69	<0.001
Gender (male)	0.73	0.53–1.02	0.06	0.95	0.77–1.16	0.60
Race			<0.001			0.003
Caucasian	1	Reference		1	Reference	
Asian	0.49	0.24–0.98	0.04	0.81	0.58–1.15	0.24
ATSI	4.35	2.10–9.01	<0.001	1.90	1.33–2.70	<0.001
MP	0.82	0.40–1.71	0.60	1.10	0.70–1.73	0.68
Other	8.74	-	1.0	1.37	0.64–2.94	0.41
BMI (kg/m^2)	0.98	0.95–1.02	0.29	1.01	0.99–1.03	0.37
Smoking status			0.01			0.01
Non-smoker	1	Reference		1	Reference	
Current smoker	1.44	0.84–2.47	0.19	1.51	1.16–1.98	0.003
Former smoker	1.63	1.18–2.25	0.003	1.11	0.90–1.36	0.34
Diabetes mellitus	1.69	1.07–2.68	0.03	1.03	0.78–1.36	0.84
Cardiovascular disease	1.94	1.39–2.72	<0.001	1.69	1.38–2.07	<0.001
Chronic lung disease	1.45	0.91–2.33	0.12	1.29	1.00–1.67	0.05
Primary renal disease			0.01			0.01
Glomerulonephritis	1	Reference		1	Reference	
Diabetic nephropathy	1.99	1.16–3.41	0.01	1.64	1.16–2.32	0.005
Hypertension	1.63	0.90–2.97	0.11	1.13	0.79–1.62	0.50
Polycystic kidney disease	0.81	0.49–1.32	0.39	1.15	0.86–1.53	0.36
Other	1.53	1.01–2.31	0.04	1.46	1.14–1.88	0.003
Late referral to nephrologists	1.31	0.84–2.03	0.23	1.01	0.80–1.29	0.91
Dialysis vintage	1.08	1.00–1.16	0.04	1.07	1.02–1.11	0.002
Last modality of KRT			0.10			0.74
Hemodialysis	1	Reference		1	Reference	
Peritoneal dialysis	1.16	0.81–1.64	0.42	1.01	0.82–1.25	0.92
Pre-emptive transplant	0.66	0.41–1.07	0.09	1.51	0.54–4.22	0.44
PRA status			0.005			0.048
0%	1	Reference		1	Reference	
1–<20%	0.71	0.50–1.02	0.07	0.94	0.75–1.17	0.56
20 – <50%	1.17	0.69–2.00	0.57	1.22	0.87–1.70	0.25
≥50%	1.90	1.10–3.26	0.02	1.39	1.02–1.90	0.04
HLA mismatch			0.42			0.94
1–2	1	Reference		1	Reference	
3–4	0.75	0.48–1.16	0.20	0.95	0.72–1.27	0.74
5–6	0.82	0.50–1.34	0.42	0.96	0.70–1.32	0.81
KDRI scores		-		1.61	1.35–1.92	<0.001
% patients transplanted and followed up in the same center			0.09			0.08
<28%	0.59	0.30–1.17	0.13	0.59	0.36–0.98	0.04
28–60 %	1	Reference		1	Reference	
>60%	1.40	0.91–2.15	0.13	1.12	0.76–1.65	0.58
Center size			0.02			0.08
<35	0.48	0.28–0.81	0.006	0.70	0.48–1.03	0.07
35–104	1	Reference		1	Reference	
>104	2.10	0.84–5.23	0.11	1.95	0.89–4.29	0.07

Table 2. Continued.

Variables	Living donor transplant			Deceased donor transplant		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Average total ischemic time			0.004			0.03
<12 h	0.53	0.33–0.87	0.01	0.66	0.40–1.06	0.09
12–14 h	1	Reference		1	Reference	
>14 h	1.76	1.02–3.04	0.04	1.47	0.96–2.23	0.07
Random center effect	<0.01			0.04	0.01–0.17	

The unadjusted and Bonferroni adjusted (for 12 models) *P*-values for the model Wald chi-square tests were, respectively, <0.0001 and < 0.002.

ATSI, Aboriginal and Torres Strait Islander; HLA, human leukocyte antigen; KDRI, kidney donor risk index; MP, Maori and Pacific Islanders; PRA, panel reactive antibody; KRT, kidney replacement therapy.

(>50%). However, polycystic kidney disease as a cause of ESKD had lower graft failure compared with glomerulonephritis (Table 3).

Death-censored graft failure

A total of 227 (8%) patients experienced death-censored graft failure during the study period (Table S1). The center 5-year death-censored graft survival varied 1.26-fold from 79.2% to 100% across centers. Variation in the hazards of death-censored graft failure across centers was increased by 4% after adjusting for patient-level characteristics, whereas there was no additional reduction in variation after adjusting for center-level characteristics. Centers with average total ischemic times for deceased donor transplants of <12 h were associated with a higher hazard of death-censored graft failure compared with centers with average total ischemic times of 12 to 14 h (HR 1.67, 95% CI 1.11–2.51). Patient characteristics associated with death-censored graft failure were younger age and race (ATSI).

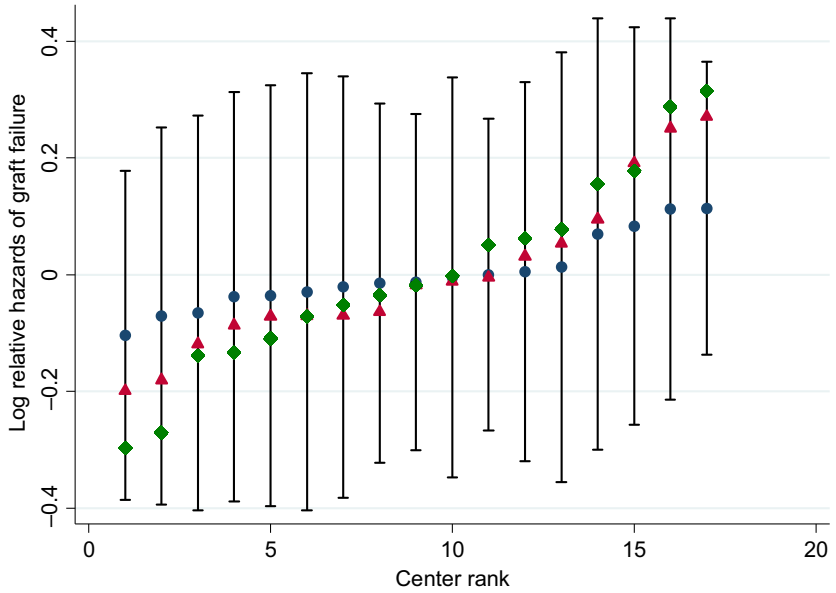

Figure 3 Log relative hazards of graft failure for deceased donor kidney transplant across 17 centers, unadjusted (diamonds), adjusted for patient-level characteristics (triangles), and adjusted for patient- and center-level characteristics (circles). Estimates are shown with 95% confidence intervals for patient- and center-level characteristics adjusted model. The transplant centers are ranked by the log relative hazards of graft failure.

Delayed graft function

A total of 85 (3%) patients experienced delayed graft function during the study period (Table S1). The center delayed graft function (DGF) varied for 7.2-fold from 1.30% to 9.38% across 17 Australian and New Zealand centers. Variation in the odds of DGF across centers was reduced by 4% after adjusting for

Table 3. Multilevel parametric survival model for living and deceased donor kidney transplant graft failure.

	Living donor transplant			Deceased donor transplant		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (decade)	1.00	0.92–1.09	0.95	1.02	0.95–1.10	0.52
Gender (male)	0.95	0.76–1.19	0.67	1.00	0.86–1.17	0.99
Race			0.006			0.004
Caucasian	1	Reference		1	Reference	
Asian	0.89	0.60–1.32	0.56	0.98	0.77–1.25	0.87
ATSI	2.96	1.54–5.68	0.001	1.70	1.28–2.26	<0.001
MP	1.32	0.84–2.06	0.23	1.30	0.94–1.80	0.12
Other	0.24	0.03–1.73	0.16	1.15	0.65–1.80	0.62
BMI (kg/m^2)	1.00	0.97–1.02	0.65	1.01	0.99–1.02	0.35
Smoking status			0.03			0.006
Non-smoker	1	Reference		1	Reference	
Current smoker	1.39	0.98–1.98	0.07	1.37	1.12–1.69	0.002
Former smoker	1.31	1.04–1.65	0.02	1.19	1.01–1.40	0.04
Diabetes mellitus	1.26	0.86–1.84	0.23	1.13	0.91–1.41	0.27
Cardiovascular disease	1.48	1.13–1.94	0.005	1.46	1.24–1.72	<0.001
Chronic lung disease	1.21	0.82–1.80	0.34	1.21	0.97–1.49	0.09
Primary renal disease			0.006			0.07
Glomerulonephritis	1	Reference		1	Reference	
Diabetic nephropathy	1.47	0.93–2.34	0.10	1.14	0.86–1.50	0.36
Hypertension	1.20	0.75–1.93	0.45	1.01	0.75–1.35	0.95
Polycystic kidney disease	0.65	0.45–0.93	0.02	0.95	0.75–1.20	0.66
Other	1.26	0.97–1.64	0.08	1.28	1.06–1.54	0.009
Late referral to nephrologists	1.37	1.03–1.82	0.03	1.07	0.90–1.27	0.49
Dialysis vintage	1.05	1.0–1.11	0.06	1.03	1.00–1.07	0.03
Last modality of KRT			0.28			0.97
Hemodialysis	1	Reference		1	Reference	
Peritoneal dialysis	1.13	0.87–1.47	0.36	1.02	0.87–1.20	0.81
Pre-emptive transplant	0.86	0.63–1.16	0.31	1.03	0.38–2.82	0.95
PRA status			0.01			0.002
0%	1	Reference		1	Reference	
1 - <20%	0.93	0.73–1.19	0.56	1.05	0.88–1.25	0.60
20 – <50%	1.43	0.99–2.07	0.06	1.41	1.09–1.83	0.01
≥50%	1.68	1.11–2.54	0.01	1.49	1.16–1.91	0.002
HLA mismatch			0.95			0.43
1–2	1	Reference		1	Reference	
3–4	0.98	0.71–1.33	0.88	1.14	0.90–1.45	0.29
5–6	1.01	0.71–1.45	0.94	1.19	0.92–1.54	0.20
KDRI scores				1.87	1.63–2.14	<0.001
% patients transplanted and followed up in the same center			0.67			0.06
<28%	0.96	0.63–1.46	0.86	0.67	0.49–0.94	0.02
28–60 %	1	Reference		1	Reference	
>60%	1.14	0.85–1.52	0.39	0.94	0.72–1.22	0.63
Center size			0.14			0.37
<35	0.74	0.53–1.03	0.08	0.95	0.74–1.21	0.66
35–104	1	Reference		1	Reference	
>104	0.95	0.54–1.70	0.87	1.42	0.86–2.33	0.17
Average total ischemic time			0.15			0.33

Table 3. Continued.

Variables	Living donor transplant			Deceased donor transplant		
	HR	95% CI	*P* value	HR	95% CI	*P* value
<12 h	1.11	0.81–1.53	0.51	0.82	0.61–1.11	0.20
12–14 h	1	Reference		1	Reference	
>14 h	1.41	0.99–2.00	0.06	1.11	0.83–1.48	0.50
Random center effect	<0.01	-		0.01	0.001–0.12	

The unadjusted and Bonferroni adjusted (for 12 models) *P*-values for the model Wald chi-square tests were, respectively, <0.0001 and <0.002.

ATSI, Aboriginal and Torres Strait Islander; HLA, human leukocyte antigen; KDRI, kidney donor risk index; MP, Maori and Pacific Islanders; PRA, panel reactive antibody; KRT, kidney replacement therapy

patient-level characteristics, but there was no additional change after adjusting for center-level characteristics. The patient characteristics of lesser HLA mismatch and prior transplant as initial KRT modality were associated with lower odds of delayed graft function (Table S5). A center characteristic significantly associated with a higher odd of DGF was center size, with small centers having a higher odd of DGF (OR 2.05, 95% CI 1.05–4.00) compared with average-sized centers.

Acute rejection

A total of 711 (26%) patients developed acute rejection during the study period (Table S1). The center acute rejection rate varied for 5.69-fold from 7.31% to 41.67% across 17 centers. Variation in the odds of acute rejection across centers was increased by 12% after adjusting for patient-level characteristics, whereas it was reduced by 26% after adjusting for center-level characteristics. However, no specific center characteristics were associated with acute rejection. The patient characteristics associated with acute rejection were younger age, current and former smoking, higher BMI, presence of cardiovascular disease and a greater number of HLA mismatches. However, presence of cardiovascular disease and late nephrologist referral were associated with lower odds of acute rejection (Table S5).

Death with functioning graft

A total of 143 (5%) patients died with functioning graft during the study period (Table S1). The center death with functioning graft rate varied 9.37-fold from 0% to 9.37% across 17 centers in Australia and New Zealand. Variation in the risk of death with functioning graft across centers was reduced by 13% after adjusting for patient-level characteristics, but there was no change in variation after adjusting for center characteristics. Small centers were associated with a lower odd of death with functioning graft (OR 0.45, 95% CI 0.25–0.82) compared with average center size. Centers with average total ischemic times for deceased donor transplants of <12 h were associated with lower odds of death with functioning graft (OR 0.40, 95% CI 0.23–0.71) compared with centers with average total ischemic times of 12–14 h. Death with functioning graft was associated with older age, presence of cardiovascular disease, higher PRA percentage, and higher number of HLA mismatches (Table S5).

Discussion

The present study demonstrated appreciable variations in mortality, graft failure, and other clinical outcomes between kidney transplant centers. For deceased donor kidney transplants, variations in mortality and graft failure were more markedly reduced following adjustment for center characteristics than for patient characteristics (41% and 55% reductions). On the other hand, such "center effects" were not apparent for mortality and graft failure following living donor kidney transplants. The principal, modifiable center characteristic associated with lower mortality rates for both deceased and living donor transplants was shorter total ischemic times (<12 h). Small center size (<35 kidney transplants/year) was also associated with a lower hazard of mortality for living donor kidney transplants. No center characteristics were associated with graft

failure for either deceased or living donor kidney transplants.

These findings support and extend those of Tsampalieros et al. [18], who recently conducted a systematic review of 24 observational studies (mostly data registries) involving 4547 kidney transplant recipients from USA, Canada, Europe, South Africa, and Asia. Significant center variation was observed in the majority of studies reporting on patient survival (five of seven studies) and graft survival (12 of 15 studies). Although this variation was not solely explained by patient factors, there was no conclusive evidence that any specific center characteristic was associated with transplant outcomes. Center volume (size) was the most common variable evaluated (patient survival four studies, graft survival 17 studies), but yielded inconsistent results. The only other characteristics that were assessed with inconclusive findings were provider experience (one study) [19], center type (for-profit versus teaching) (one study) [19], percentage of pediatric cases (one study) [20], rural versus non-rural post-transplant caring center (one study) [21], and cross-match policy (one study) [21]. In addition to the evaluation of only a very limited number of center characteristics, this systematic review was also appreciably limited by substantial clinical, methodologic, and statistical heterogeneity, which precluded meta-analysis of the data. Most studies performed limited multivariable adjustment, and all studies included patients prior to 2000, such that no study was able to evaluate transplant center effects in the modern era of immunosuppression, as was able to be done in the present study. This latter point is particularly relevant given that a study by Gjertson et al. [20] reported that the association of transplant center effects with patient survival decreased with calendar year between the 1980s and 1990s. Finally, no previous study has comprehensively and separately analyzed living and deceased donor kidney transplant outcomes for associations with center characteristics even though these forms of kidney transplantation are very different in terms of their nature and outcomes.

In the systematic review by Tsampalieros et al. [18], 17 studies examined a relationship between center size and graft survival, of which eight reported improved graft survival with larger center size, five found no association and four were inconclusive. There was, however, marked heterogeneity with respect to center size categorization, analytic methods used, and reporting of outcomes. The associations between larger center size and better patient outcomes have been reported in the dialysis setting [16,22]. One previous study of the effect of transplant volume and patient case mix on variation transplant outcomes across 5 centers in Canada reported that center volume or case mix was not responsible for the differences in patient or graft survival [23]. In that study, living and deceased donor kidney transplants were analyzed together and center volume was the only center characteristics involved in the study. However, in the present study, when living and deceased donor kidney transplants were analyzed separately, center size was associated with mortality for living donor transplants but not with deceased donor kidney transplants. The reason for better outcomes with small centers was unclear, but might be due to selection of lower risk living donor kidney transplants in small centers. Although the study adjusted for a number of patient and transplant characteristics, residual confounding was still possible.

In the present investigation, the contribution of center characteristics to variations in kidney transplant patient and graft survival rates was greater, compared with patient characteristics, for deceased donor transplants than for living donor transplants. This finding may be related to key differences between living and deceased kidney transplantation, such as the nature of the surgery (elective versus unplanned/urgent), selection of donors and recipients, and variations in ischemic times (relatively short with a narrow range versus relatively long with a wide range). It is also possible that center effects may have been more difficult to elucidate in living donor kidney transplants due to lower event rates, given that living donor kidney transplants are associated with lower rates of graft loss [24,25].

Another novel finding of the present study was that a lower center average total ischemic time was associated with lower mortality of both deceased and living kidney transplant recipients. Although ischemic time at the individual level has been well-recognized as a risk factor for graft survival [26], a center's average total ischemic time has not been explored as a modifiable risk fact for transplant center outcomes. This center characteristic likely reflects the quality, organization, and performance of a transplant team in a center, and our study's findings suggest that it might be useful as a key performance indicator for transplant centers.

The strengths of the present study included its comprehensive analysis of a large range of patient characteristics, center characteristics, and transplant outcomes. It included all centers in Australia and New Zealand thereby mitigating the risk of ascertainment bias and improving generalizability. It is also the first study to separately analyze living and deceased donor kidney transplants for the relationship between center effects

and patient-level outcomes. Moreover, the study used robust statistical methodology, including both fixed and random center effects in its modeling.

These strengths should be balanced against the study's limitations, which included the possibilities of residual confounding and coding bias. The limited data collected by the ANZDATA registry prevented inclusion and analysis of important patient characteristics (level of education, treatment adherence, severity of comorbidities, distance from transplant center, etc.) and center characteristics (staffing levels, frequency of post-transplant follow-up visits, type and target level of immunosuppressant used, proportion of patients achieving adequate immunosuppressant drug levels, center protocols, infection control processes, continuous quality improvement processes, frequency of multidisciplinary governance meetings, etc.). Finally, the results of this study may not be generalizable outside of Australia and New Zealand or to the management of multiple kidney transplants, highly sensitized patients or ABO-incompatible kidney transplants.

In conclusion, the present study demonstrated that there was appreciable variation in clinical outcomes across kidney transplant centers, particularly for deceased donor kidney transplants in Australia and New Zealand. The variation was not solely explained by patient characteristics and variation in patient and graft survival for deceased donor kidney transplants was largely attributable to center characteristics. Of the specific center characteristics examined, lower center average total ischemic times were associated with lower hazards of mortality in both living and deceased donor transplant recipients. Center size was generally not associated with transplant outcomes, except that small center size was associated with a lower hazard of mortality for living donor kidney transplants. It is possible that addressing transplant center effects (e.g., by standardizing unit practices or expertise) may improve outcomes. Future studies should aim to examine center characteristics at a more granular level to try to identify specific modifiable center practices and organization characteristics that are associated with superior kidney transplant outcomes.

Authorship

HH and DWJ: wrote the draft. HH and EMP: analyzed data. HH, EMP, YC, CMH, SBC, and DWJ: participated in study design, interpretation of data, and all authors reviewed, revised the draft, and approved the final version of the manuscript.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Total number of events for each outcome for living and deceased donor transplants.

Table S2. The standard deviations as a measure of variation in the random center outcome values (log relative hazards) from multivariable models of primary and secondary outcomes.

Table S3. Multilevel parametric survival model for living and deceased donor kidney transplant death-censored graft failure.

Table S4. Multivariable logistic regression of deceased donor kidney transplant secondary outcomes.

Table S5. Multivariable logistic regression of living donor kidney transplant secondary outcomes.

Figure S1. Kaplan Meier survival estimates for deceased donor kidney transplant recipients by individual centers.

Figures S2. Kaplan Meier graft survival estimates for deceased donor kidney transplants by individual centers.

Figure S3. Kaplan Meier survival estimates for living donor kidney transplant recipients by individual centers.

Figures S4. Kaplan Meier graft survival estimates for living donor kidney transplants by individual centers.

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