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ORIGINAL ARTICLE

Association of prevalent vascular disease with allograft failure and mortality in live-donor kidney transplant recipients – a retrospective cohort study

Rahul Mainra[1,2], Germaine Wong[3,4,5], Helen Pilmore[6,7] & Wai H. Lim[1,8]

1 Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia
2 Division of Nephrology, Saskatchewan Transplant Program, St. Paul's Hospital, University of Saskatchewan, Saskatoon, SK, Canada
3 Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia
4 School of Public Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia
5 Department of Renal Medicine, Westmead Hospital, Sydney, NSW, Australia
6 Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand
7 Department of Medicine, Auckland University, Auckland, New Zealand
8 School of Medicine, University of Western Australia, Perth, WA, Australia

Correspondence
Rahul Mainra MD, MMed, FRCPC, FRACP, Division of Nephrology, Saskatchewan Transplant Program, St. Paul's Hospital, University of Saskatchewan, 1702 20th Street West, Saskatoon, SK S7M 0Z9, Canada.
Tel.: 306-655-5936;
fax: 306-655-5959;
e-mail: rahul.mainra@usask.ca

SUMMARY

Limited data exist regarding the impact of prevalent vascular disease after live-donor kidney transplantation. We aimed to determine the associations between the number of prevalent vascular diseases, allograft, and patient outcomes following live-donor transplantation. This cohort study used data from the Australia and New Zealand Dialysis and Transplant Registry. Rates between recipients of live-donor kidney transplants ± prevalent vascular disease prior to transplantation were calculated. The associations between vascular disease, allograft failure, and all-cause mortality were assessed using Cox regression modeling. Kaplan–Meier proportions were used to calculate all-cause mortality and death with a function graft stratified by vascular disease burden. Of 4742 live-donor recipients, 428 (9%) and 84 (2%) had prevalent vascular disease at 1 and ≥2 sites, respectively. Compared to recipients without vascular disease, the respective adjusted hazard ratios (95% confidence intervals) for patients with vascular disease at 1 and ≥2 sites were 1.78 (1.41–2.25) and 3.02 (2.03–4.50) for all-cause mortality; and 1.54 (1.26–1.88) and 2.28 (1.54–3.38) for allograft failure. All-cause mortality in recipients with vascular disease at 0, 1 and ≥2 sites was 0.028 (0.025, 0.031), 0.090 (0.073, 0.106) and 0.247 (0.196, 0.282) over the first 5-year post-transplant. There was an incremental association between the number of prevalent vascular disease sites and risk of allograft failure and all-cause mortality in live-donor kidney transplant recipients.

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Introduction

Kidney transplantation is the treatment of choice for many patients with end-stage kidney disease (ESKD) because it confers a significant survival advantage and improves quality of life compared to maintenance dialysis [1]. Recipients of live-donor allografts report 5-year patient survival of 90–96% compared to 81–90% for recipients of deceased donor allografts. Consequently, clinicians would preferentially advocate live-donor kidney transplants for patients with ESKD where possible. These improved outcomes are likely attributed to the avoidance of the deleterious effects of prolonged waiting times and shorter cold ischemic time [2]. However, comorbidities that are well known to affect patient survival, such as diabetes and vascular disease, may attenuate the expected survival benefits associated with live-donor transplantation.

Several pretransplant comorbidity scores have been developed to estimate post-transplant survival and assist clinicians in the decision-making process of determining transplant suitability for deceased donor wait-listing [3]. Prevalent vascular disease burden and vascular risk factors are included as key covariates in many of these prediction models for estimating post-transplant survival after deceased donor transplantation [3–5]. Recent work has also shown that incremental vascular disease burden prior to transplantation was associated with substantially poorer patient survival [6]. Such prediction models do not exist for recipients of live-donor kidney transplants given the well accepted improvement in outcomes compared with deceased donor. However, the impact of pre-existing vascular disease on longer term outcomes may be different because of the shorter accrued dialysis times and the avoidance of cumulative dialysis-related vascular complications. This information may be valuable to both physician and patient during the decision process of live or deceased donor kidney transplantation. Thus, the primary aim of this study was to determine the impact of prevalent vascular disease burden on long-term patient and allograft outcomes following live-donor kidney transplantation. We also aimed to determine if donor types modified the relationship between prevalent vascular disease burden and mortality after kidney transplantation.

Materials and methods

Study population

In the primary analyses, data of primary adult (aged ≥18 years) live-donor kidney transplant recipients in Australia and New Zealand between 1980 and 2014 were extracted from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. Recipients of multiple-organ transplants were excluded. Recipients with no recorded vascular disease status at time of transplant were also excluded (n = 545) (Fig. S1).

In the secondary analyses, we also included primary adult (aged ≥18 years) deceased donor kidney transplant recipients between 1980 and 2014 to allow comparison with the cohort of live-donor kidney transplant recipients in the same time period (1980–2014).

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism." The reporting of this study conforms to the STROBE statement [7] and is presented in Table S1 and Fig. S1. Approval of study by research ethics committee and informed consents were not required because only de-identified information was utilized for analysis. However, consents for inclusion in the ANZDATA registry, which include the use of data for research were sought from all patients with ESKD in Australia and New Zealand.

Exposure factor

The exposure factor was prevalent vascular disease burden prior to kidney transplantation, which ANZDATA registry collects information on the presence or absence of disease at three sites: coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD). Vascular disease burden of each recipient was categorized according to the number of sites affected by vascular disease prior to transplantation, that is, 0, 1 or at least 2 sites of prevalent vascular diseases. ANZDATA registry does not verify the accuracy of the reporting of vascular disease nor does it collect data on the severity of vascular disease at each site.

Clinical outcomes

The primary outcome of this study was all-cause mortality; with secondary outcomes of death with a functioning graft, overall allograft failure (death or returned to dialysis), death censored allograft failure and cause-specific mortality [including cardiovascular disease (CVD), infection and cancer-related mortality]. All analyses performed were prespecified *a priori*.

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Baseline data

Baseline characteristics included donor factors of age and gender; recipient factors of age, gender, ethnicity, body mass index (BMI), primary causes of ESKD, peak percentage panel reactive antibody, waiting time, and prevalent diabetes status; and transplant-related factors of human leukocyte antigen (HLA)-mismatches, total ischemic time, induction therapy and initial immunosuppression [prednisolone, calcineurin inhibitors (CNI) and anti-metabolite agents]. Transplant era was categorized into four groups for analysis (i.e. 1980–1988, 1989–1996, 1997–2005, and 2006–2014).

Primary analyses

Baseline data of the study cohort of the live-donor recipients were expressed as number (proportion), mean ± standard deviation (SD) or median and interquartile range (IQR); with comparisons examined by chi-square test, analysis of variance (ANOVA), and Kruskal-Wallis nonparametric test, respectively. The associations between prevalent vascular disease sites and clinical outcomes were examined using Cox proportional hazard regression analysis, with results expressed as adjusted hazard ratio (HR) and 95% confidence interval (CI). Prespecified covariates included in the model included donor and recipient age, diabetes, total ischemic time, era, ethnicity, waiting time, smoking history, and BMI. The proportional hazard assumptions of all Cox regression models were checked graphically by plotting the Schoenfeld residuals, with no evidence of departures from proportional hazards for each outcome. Covariates with *P*-values of less than 0.1 in the unadjusted models were included in the adjusted models, although donor and recipient age, waiting time, diabetes status, smoking history, and era were included in all models given their established biological relationships with mortality and/or allograft failure. Two-way interactions between vascular disease sites and other covariates including diabetes status, smoking history, and era were examined for each outcome. All-cause mortality and death with a functioning graft were calculated using Kaplan–Meier proportions for the predefined periods of 0–1, >1–5 and >5–10 years post-transplant according to the number of vascular disease sites.

We conducted a competing risk regression for cause-specific mortality of CVD, infection and cancer mortality taking into account the informative nature of censoring because of the competing risk of non-CVD, noninfection and noncancer-related mortality, respectively, using the method of Fine and Gray [8]. The stratified proportional sub-distributional HRs were calculated to estimate the covariate effects on the cumulative incidence function. Covariates included in the competing risk models were identical to the Cox regression models.

Secondary analyses

We also conducted two-way interaction analyses between donor types (living and deceased donor status) and vascular disease burden for all-cause mortality and death with a functioning graft, with *P*-values of <0.05 considered significant interactions. Sensitivity analyses were conducted to examine the association of site-specific vascular disease and all-cause mortality, death with a functioning graft and death censored allograft failure. Statistical evaluation was performed by STATA version 11. *P*-values of <0.05 were considered statistically significant.

Results

Table 1 describes the baseline characteristics according to the vascular disease burden pretransplantation. Of 4742 live-donor kidney transplant recipients, 4230 (89.2%) recipients had no prevalent vascular disease at the time of transplant, while 428 (9.0%) and 84 (1.8%) had vascular disease at 1 and ≥2 sites, respectively. The median (IQR) allograft and patient follow-up periods for the study cohort were 6.8 (8.0) and 7.8 (9.1) years; resulting in 38 249 and 44 020 allograft and patient-years of exposure, respectively.

All-cause mortality and death with a functioning graft

Compared to recipients without prevalent vascular disease, all-cause mortality at all time points was significantly higher in recipients with any vascular disease(s) (Table 2). Between 0–1 and >1–5 years post-transplant, the proportion of recipients (95% CI) suffering all-cause mortality with ≥2 vascular disease sites were 0.110 (0.059, 0.202) and 0.247 (0.196, 0.282), respectively; compared to 0.009 (0.006, 0.012) and 0.028 (0.025, 0.031) for recipients without prevalent vascular disease. Similar trends for death with a functioning graft by vascular disease burden are shown in Table 2.

Association between vascular disease burden and all-cause mortality in live-donor kidney transplant recipients

Compared to recipients without prevalent vascular disease, the adjusted HR for all-cause mortality in those

Table 1. Baseline characteristic of live-donor kidney transplant recipients stratified by vascular disease burden between 1980 and 2014 (n = 4742).

	No vascular disease (n = 4230)	1 vascular disease site (n = 428)	≥2 vascular disease sites (n = 84)	*P*-value
Demographics				
Age (years, mean ± SD)	41.2 ± 13.5	51.0 ± 12.0	53.9 ± 10.5	<0.001
Male (n, %)	2546 (60.2)	306 (71.5)	58 (69.0)	<0.001
Race (n, %)				
Caucasian	3487 (82.4)	355 (82.9)	68 (81.0)	0.213
Indigenous	139 (3.3)	22 (5.1)	4 (4.8)	
Others	604 (14.3)	51 (12.0)	12 (14.2)	
Diabetes (n, %)				
None	3941 (93.3)	292 (68.4)	38 (45.2)	<0.001
Pretransplant	284 (6.7)	135 (31.6)	46 (54.8)	
Coronary artery disease (n, %)	0 (0.0	279 (65.2)	80 (95.2)	<0.001
Peripheral vascular disease (n, %)	0 (0.0)	71 (16.6)	64 (76.2)	<0.001
Cerebrovascular disease (n, %)	0 (0.0)	78 (18.2)	36 (42.9)	<0.001
Body mass index (kg/m^2, mean ± SD)	25.0 ± 5.1	26.3 ± 4.9	26.6 ± 4.8	<0.001
Waiting time (years, mean ± SD)	1.1 ± 1.6	1.8 ± 2.1	2.3 ± 2.5	<0.001
Smoker (n, %)				
Nonsmoker	2620 (64.5)	224 (52.6)	35 (42.2)	<0.001
Former smoker	1103 (27.1)	171 (40.1)	40 (48.2)	
Current smoker	340 (8.4)	31 (7.3)	8 (9.6)	
Cause of ESKD (n, %)				
Glomerulonephritis	2174 (51.4)	158 (36.9)	21 (25.0)	<0.001
Diabetes	169 (4.0)	101 (23.6)	40 (47.6)	
Cystic	587 (13.9)	82 (19.2)	9 (10.7)	
Analgesic nephropathy	25 (0.6)	4 (0.9)	0 (0.0)	
Vascular	159 (3.8)	34 (7.9)	9 (10.7)	
Reflux nephropathy	547 (12.9)	16 (3.7)	1 (1.2)	
Others	569 (13.4)	33 (7.8)	4 (4.8)	
Donor characteristics				
Age (years, mean ± SD)	47.6 ± 11.7	50.7 ± 11.2	50.5 ± 11.3	<0.001
Male (n, %)	1803 (43.2)	159 (37.6)	36 (42.9)	0.085
Immunology/transplant				
HLA-ABDR mismatches (mean ± SD)	2.9 ± 1.6	3.4 ± 1.6	3.5 ± 1.7	<0.001
Peak PRA > 50% (n, %)	200 (5.1)	23 (5.6)	9 (11.3)	0.180
Ischemic time (h, mean ± SD)	2.4 ± 1.8	2.6 ± 1.5	2.9 ± 1.6	0.009
Induction (n, %)	2269 (53.6)	273 (63.8)	52 (61.9)	<0.001
Transplant era (n, %)				
1980–1988	169 (4.0)	5 (1.2)	0 (0.0)	<0.001
1989–1996	457 (10.8)	23 (5.4)	4 (4.8)	
1997–2005	1497 (35.4)	140 (32.7)	24 (28.6)	
2006–2014	2107 (49.8)	260 (60.7)	56 (66.6)	
Initial immunosuppressive agents*				
Calcineurin inhibitors (n, %)				
Cyclosporine	2204 (52.1)	195 (45.6)	42 (50.0)	0.011
Tacrolimus	1699 (40.2)	205 (47.9)	38 (45.3)	
Not recorded	327 (7.7)	28 (6.5)	4 (4.7)	

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Table 1. Continued.

	No vascular disease (n = 4230)	1 vascular disease site (n = 428)	≥2 vascular disease sites (n = 84)	P-value
Anti-metabolite agents (n, %)				
Azathioprine	715 (16.9)	33 (7.8)	5 (6.0)	<0.001
Mycophenolate†	3120 (73.8)	370 (86.4)	71 (84.5)	
Not recorded	395 (9.3)	25 (5.8)	8 (9.5)	

ESKD, end-stage kidney disease; HLA, human leukocyte antigen; PRA, panel reactive antibody.

Data expressed as number (proportion) or as mean ± SD.

*All recipients were initiated on prednisolone.

†Includes both mycophenolate mofetil and enteric-coated mycophenolic acid formulations.

Table 2. Proportion of patients with death with a functioning graft and all-cause mortality stratified by vascular disease burden in live-donor kidney transplant recipients.

	Deaths per 1000 patients		
	0–1 years*	>1–5 years*	>5–10 years*
All-cause mortality			
Vascular disease burden			
0 site pretransplant	0.009 (0.006, 0.012)	0.028 (0.025, 0.031)	0.053 (0.049, 0.058)
1 site pretransplant	0.031 (0.018, 0.053)	0.090 (0.073, 0.106)	0.218 (0.190, 0.246)
≥2 sites pretransplant	0.110 (0.059, 0.202)	0.247 (0.196, 0.282)	0.112 (0.094, 0.123)
Death with functioning graft			
Sites of vascular disease			
0 site pretransplant	0.006 (0.004, 0.009)	0.022 (0.019, 0.025)	0.045 (0.040, 0.050)
1 site pretransplant	0.032 (0.019, 0.054)	0.065 (0.051, 0.079)	0.182 (0.150, 0.216)
≥2 sites pretransplant	0.101 (0.052, 0.191)	0.209 (0.157, 0.253)	0.081 (0.063, 0.095)

The probability of all-cause mortality and death with a functioning graft at prespecified time points post–kidney transplant was calculated using the Kaplan–Meier method.

*P < 0.001.

with 1 and ≥2 vascular disease sites was 1.84 (1.45, 2.33) and 2.99 (1.91, 4.33), respectively (Fig. 1 and Table 3). Other covariates associated with all-cause mortality are shown in Table 3. There were no interactions between vascular disease burden and diabetes status, age or era for all-cause mortality. Kaplan–Meier curves for all-cause mortality in recipients with no vascular disease compared to those with vascular disease at 1 and ≥2 sites are presented in Fig. 2a.

Association between vascular disease burden and death with a functioning graft in live-donor kidney transplant recipients

Compared to recipients without prevalent vascular disease, the adjusted HR for death with a functioning graft in those with 1 and ≥2 vascular disease sites was 1.83 (1.37, 2.44) and 2.45 (1.49, 4.03), respectively (Fig. 1 and Table 3). Other covariates associated with death with a functioning graft are shown in Table 3. There were no interactions between vascular disease burden and diabetes status, age or era for death with a functioning graft. Kaplan–Meier curves for death with a functioning graft in recipients with no vascular disease compared to those with vascular disease at 1 and ≥2 sites are presented in Fig. 2b.

Vascular disease burden, overall allograft failure, and death censored allograft failure in live-donor kidney transplant recipients

The adjusted HR for overall allograft failure in recipients with 1 and ≥2 vascular disease sites was 1.54 (1.26, 1.88) and 2.30 (1.55, 3.40), respectively compared to those without. There was no consistent association between vascular disease sites and death censored

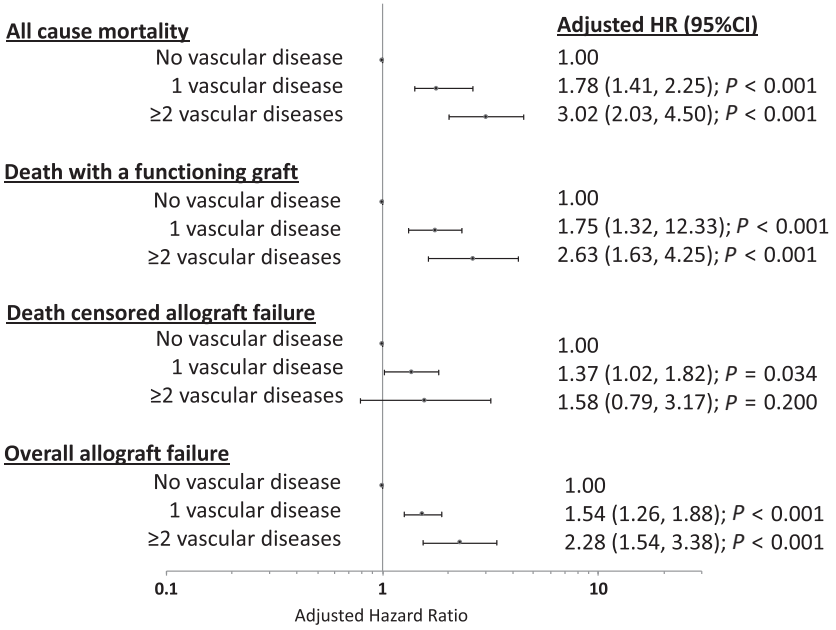

Figure 1 Unadjusted Kaplan–Meier survival curves with corresponding number at risk tables of all-cause mortality (a), death with a functioning graft (b), overall allograft failure (c) and death censored allograft failure (d), stratified by vascular disease burden (i.e. no prevalent vascular disease versus prevalent vascular disease at 1 and ≥2 sites pretransplantation), in live-donor kidney transplant recipients. Log-rank *P*-values $P < 0.001$ for all outcomes, except for death censored allograft failure ($P = 0.58$).

allograft failure (Fig. 1 and Table 3). Kaplan–Meier curves for overall allograft failure and death censored allograft failure in recipients with no vascular disease compared to those with vascular disease at 1 and ≥2 sites are presented in Fig. 2c,d, respectively. The most common cause of overall allograft failure in recipients with vascular disease at 1 and ≥2 sites was death with a functioning graft (56% and 71%, respectively), compared to 28% in those without vascular disease ($P < 0.001$, Fig. 3). There was no difference in rates of early allograft failure (up to 3 months post-transplant) in patients with no vascular disease compared to those with vascular disease at 1 and ≥2 sites (46%, 31% and 64%, respectively; $P = 0.34$).

Association between vascular disease burden and site- and cause-specific mortality in live-donor kidney transplant recipients

Compared to recipients without prevalent vascular disease, the adjusted sub-distributional HR for CVD mortality for recipients with 1 and ≥2 vascular disease sites was 1.96 (1.26, 3.06) and 3.29 (1.59, 6.80), respectively; and was 2.12 (1.15, 3.88), and 2.86 (0.96, 8.58), respectively for infection-related mortality. Similar estimates were observed for CVD-related [1 site: adjusted sub-distributional HR: 2.52 (1.43, 4.40); ≥2 sites: 3.90 (1.57, 9.66)] and infection-related [1 site: adjusted sub-distributional HR: 2.21 (1.07, 4.57); ≥2 sites: 4.43 (1.23, 15.96)] death with a functioning graft. Figure S2a,b shows the cumulative incidence curves of CVD and infection-related mortality, respectively, stratified by vascular disease burden. Infection-related mortality was due primarily to bacterial and fungal infections and increased with vascular disease burden. In patients with no vascular disease, 49% and 10% infection-related deaths were of bacterial and fungal origins. This rate increased to 53% and 11% in patients with vascular disease at 1 site and 60% and 40% ($P = 0.45$), respectively, in patients with vascular disease at ≥2 sites. There was no association between vascular disease burden and cancer mortality. In the analysis that specifically considered site-specific vascular disease, there were consistent independent associations between prevalent PVD and CAD for all-cause mortality [adjusted HR of 1.87 (1.29, 2.69) and 1.59 (1.23, 2.07), respectively] and death with a functioning graft [adjusted HR 2.01 (1.33, 3.05) and 1.52 (1.14, 2.03), respectively]. There was no association between cerebrovascular disease and all-cause mortality [adjusted HR 1.26 (0.79, 2.00)] or death with a functioning graft [adjusted HR 1.39 (0.95, 1.74)]. There was no association between sites of vascular disease and death censored allograft failure.

Interaction between donor types, vascular disease, and all-cause mortality and death with a functioning graft

The characteristics of the deceased and living donor transplant recipients are shown in Table S2. There was an interaction between donor type and vascular disease burden for all-cause mortality (*P*-value for interaction 0.009) and death with a functioning graft (*P*-value for

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Table 3. Multivariable Cox regression models of the associations between vascular disease burden, overall and death censored allograft failure, death with a functioning graft, and all-cause mortality in live-donor kidney transplant recipients.

	Adjusted hazard ratios (95% CI)			
	Overall allograft failure	Death censored allograft failure	Death with a functioning graft	All-cause mortality
Vascular disease burden				
0 site pretransplant	1.00	1.00	1.00	1.00
1 site pretransplant	1.54 (1.26, 1.88)	1.37 (1.02, 1.82)	1.75 (1.32, 2.33)	1.78 (1.41, 2.25)
≥2 sites pretransplant	2.28 (1.54, 3.38)	1.58 (0.79, 3.17)	2.63 (1.63, 4.25)	3.02 (2.03, 4.50)
Recipient age (per 10-year increase)	1.00 (0.95, 1.06)	0.75 (0.69, 0.80)	1.87 (1.69, 2.06)	1.66 (1.53, 1.79)
Donor age (per 10-year increase)	1.13 (1.07, 1.20)	1.18 (1.10, 1.26)	1.02 (0.92, 1.12)	1.03 (0.95, 1.12)
Diabetes	1.46 (1.19, 1.78)	1.30 (0.98, 1.72)	1.86 (1.39, 2.49)	1.93 (1.53, 2.44)
Waiting time (per year increase)	1.08 (1.04, 1.12)	1.05 (1.01, 1.10)	1.13 (1.08, 1.19)	1.13 (1.08, 1.18)
HLA (per mismatch increase)	1.09 (1.05, 1.14)	1.11 (1.06, 1.17)	–	–
Race				
Caucasian	1.00	1.00	1.00	1.00
Indigenous	1.85 (1.43, 2.40)	2.14 (1.57, 2.91)	1.26 (0.78, 2.06)	1.64 (1.18, 2.18)
Others	1.03 (0.84, 1.25)	1.13 (0.88, 1.43)	0.87 (0.61, 1.25)	0.76 (0.55, 1.03)
Total ischemic time (per hour increase)	1.01 (0.97, 1.06)	0.99 (0.94, 1.05)	1.04 (0.97, 1.10)	1.04 (0.98, 1.09)
Body mass index (kg/m^2)				
<18.5	1.23 (0.90, 1.68)	1.21 (0.86, 1.72)	1.19 (0.62, 2.27)	1.07 (0.65, 1.77)
18.5–24.9	1.00	1.00	1.00	1.00
25–29.9	1.19 (1.03, 1.36)	1.36 (1.15, 1.62)	0.96 (0.75, 1.23)	0.96 (0.78, 1.16)
≥30	1.13 (0.93, 1.37)	1.22 (0.95, 1.56)	1.04 (0.76, 1.42)	1.04 (0.81, 1.35)
Smoking history				
Nonsmoker	1.00	1.00	1.00	1.00
Former smoker	1.18 (1.02, 1.36)	1.15 (0.97, 1.38)	1.30 (1.03, 1.64)	1.24 (1.03, 1.50)
Current smoker	1.67 (1.39, 2.01)	1.68 (1.35, 2.09)	1.73 (1.24, 2.43)	1.59 (1.22, 2.07)
Transplant era				
1980–1988	1.00	1.00	1.00	1.00
1989–1996	1.19 (0.85, 1.67)	1.12 (0.78, 1.60)	4.13 (0.97, 17.62)	1.41 (0.83, 2.40)
1997–2005	0.76 (0.53,1.07)	0.69 (0.48, 0.99)	2.83 (0.66, 12.06)	0.95 (0.55, 1.65)
2006–2014	0.52 (0.35, 0.75)	0.49 (0.33, 0.75)	1.86 (0.43, 8.14)	0.61 (0.34, 1.10)

Data expressed as adjusted hazard ratios with 95% confidence intervals (95% CI).

HLA, human leukocyte antigen.

interaction 0.038). The proportion of patients (95% CI) with all-cause mortality and death with a functioning graft were higher for live-donor transplant recipients with ≥2 vascular disease sites compared to deceased donor recipients, with 5-year rate of all-cause mortality of 0.357 (0.255, 0.484) and 0.244 (0.196, 0.300), respectively (Table 4). For recipients of live-donor transplants with vascular disease at 0, 1 and ≥2 sites, the cumulative incidence of all-cause mortality at 5 years was 96% (96–97%), 88% (84–91%) and 64% (52–75%), respectively; compared to 92% (92–93%), 83% (81–85%) and 76% (70–80%), respectively for recipients of deceased donor transplants (log-rank $P < 0.01$). Among recipients of live-donor transplants, the respective adjusted HR for all-cause mortality and death with a functioning graft among those with vascular disease at ≥2 sites was 3.02 (1.03, 4.50) and 2.63 (1.63, 4.25), compared to those without vascular disease. Among recipients of deceased donor transplants, the respective adjusted HRs for recipients with ≥2 vascular disease sites were 1.62 (1.33, 1.97) and 1.51 (1.18, 1.94; Fig. 4).

Discussion

In recipients of live-donor kidney transplants, incremental vascular disease burden at the time of transplantation was associated with a significant survival disadvantage, with 5-year mortality rates almost 10-times greater in recipients with vascular disease at ≥2 sites compared to those without vascular disease. The

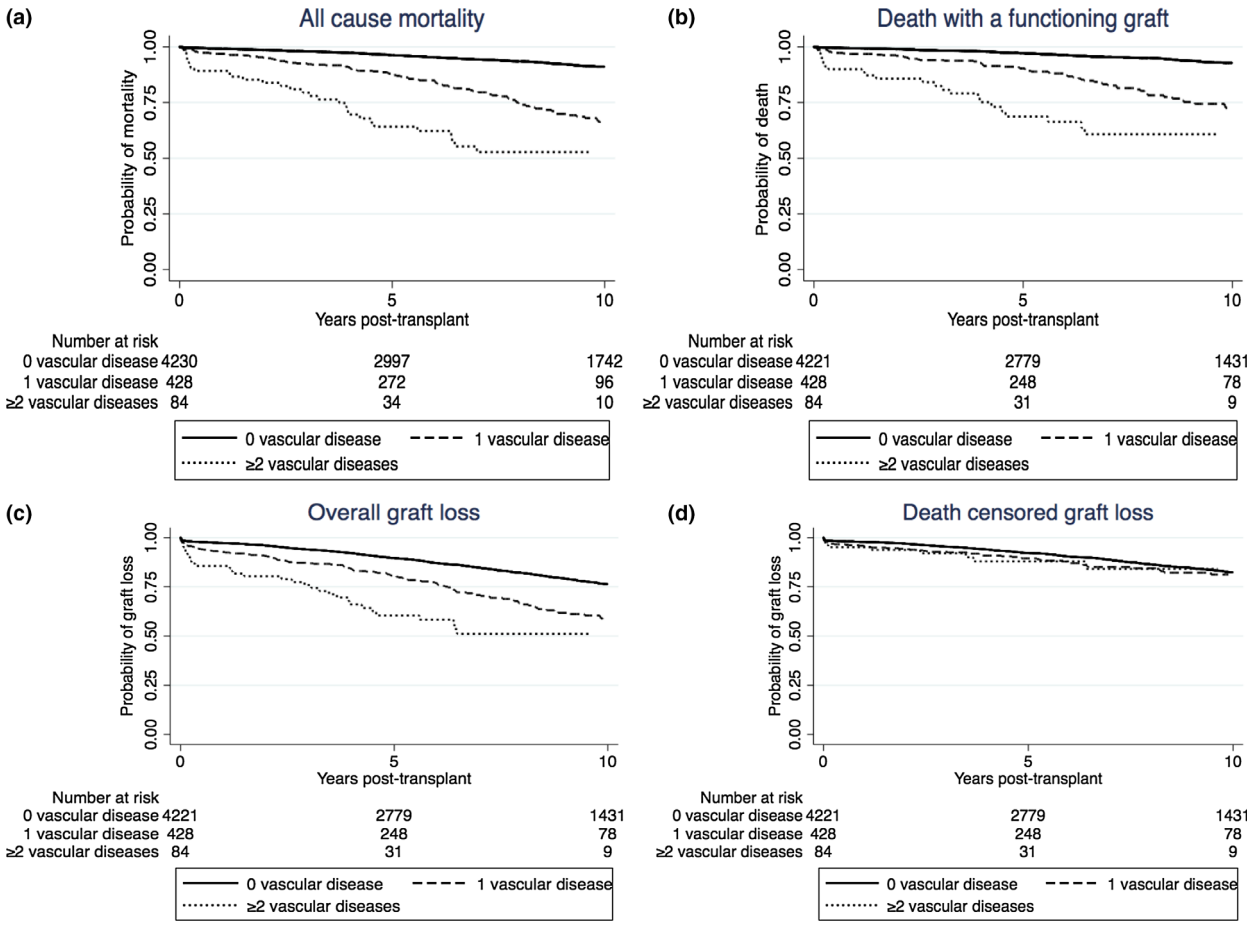

Figure 2 Forest plots showing the adjusted hazard ratios with 95% confidence intervals (95% CI) and corresponding *P*-values of the associations between vascular disease burden (i.e. no prevalent vascular disease versus prevalent vascular disease at 1 and ≥2 sites pretransplantation) and all-cause mortality, death with a functioning graft, overall allograft failure and death censored allograft failure in live-donor kidney transplant recipients.

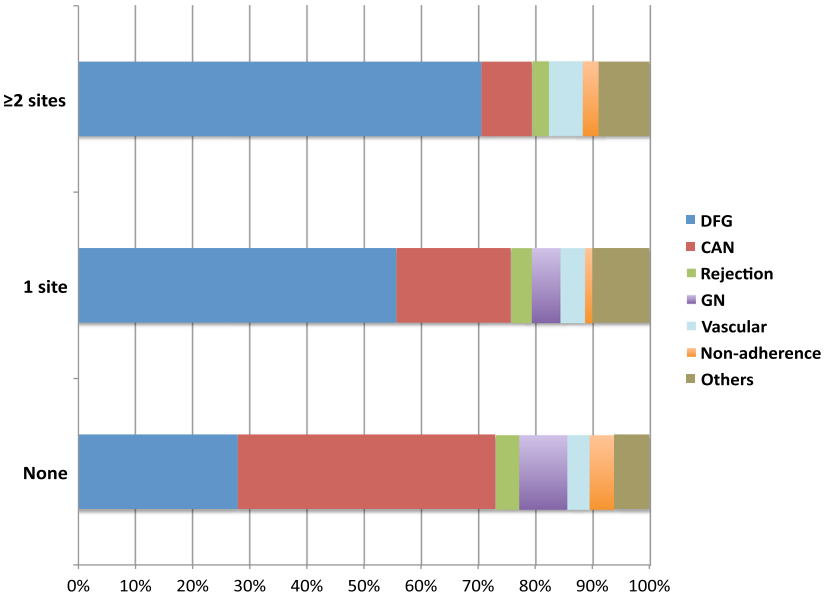

Figure 3 Bar graph showing the causes of allograft failure in live-donor kidney transplant recipients with and without prevalent vascular disease at 1 and ≥2 sites. CAN, chronic allograft nephropathy; DFG, death with a functioning graft; GN, glomerulonephritis.

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excess risk of mortality in recipients with vascular disease was predominantly attributed to CVD and infection. This association also appeared to be modified by donor types, such that the relative adverse impact of vascular disease on mortality was of greater magnitude among recipients of live-donor transplants compared to recipients of deceased donor transplants.

Several epidemiological studies have consistently shown an adverse impact of prevalent vascular disease on mortality following deceased donor kidney transplantation, although the significance of this impact in live-donor kidney transplantation remains uncertain [6,9–11]. Considering the long-term outcomes of live-donor transplant recipients are superior to those of deceased donor transplant recipients [12–15], it would be inappropriate to extrapolate data from deceased donor transplant recipients to inform clinicians advocating for their patients. Furthermore, none have quantified the interactive effects between donor type and vascular disease burden for mortality. This information is vital to guide shared clinical decision-making regarding the trade-offs of accepting a live kidney donor from a poorly matched unrelated donor or waiting for a better-matched deceased donor kidney but with variable qualities in a patient with high vascular risk burden.

Our finding that donor type was an effect modifier between vascular disease burden and mortality post-transplant is unexpected and deserves further investigation. Our study shows that the adverse association between prevalent vascular disease and mortality was of greater magnitude in recipients of live-donor transplants compared to recipients of deceased donor transplants, primarily in those with a greater burden of vascular disease (i.e. vascular disease affecting at least two sites). Even though the availability of live-donors should not

Table 4. Proportion of patients with death with a functioning graft and all-cause mortality over 5-year post-transplant stratified by vascular disease burden and donor types.

	All-cause mortality 0–5 years		Death with functioning graft 0–5 years	
	Live-donors	Deceased donors	Live-donors	Deceased donors
Vascular disease burden				
0 site pretransplant	0.037 (0.031, 0.043)	0.077 (0.071, 0.083)	0.028 (0.023, 0.034)	0.061 (0.056, 0.066)
1 site pretransplant	0.121 (0.091, 0.156)	0.169 (0.148, 0.191)	0.097 (0.070, 0.133)	0.132 (0.113, 0.154)
≥2 sites pretransplant	0.357 (0.255, 0.484)	0.244 (0.196, 0.300)	0.310 (0.209, 0.444)	0.180 (0.135, 0.238)

The probability of all-cause mortality and death with a functioning graft at prespecified time points post-kidney transplant was calculated using the Kaplan–Meier method.

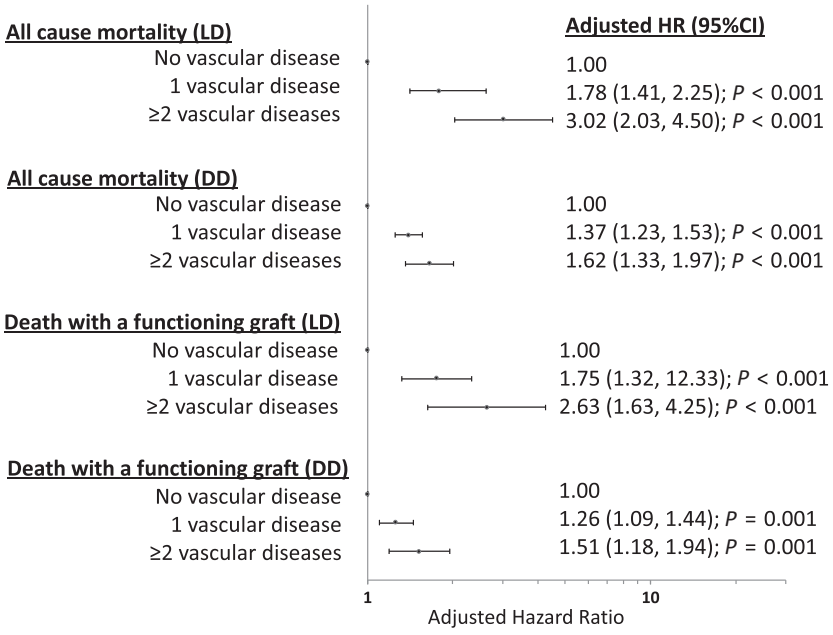

Figure 4 Forest plots showing the adjusted hazard ratios with 95% confidence intervals (95% CI) and corresponding *P*-values of the associations between vascular disease burden (i.e. no prevalent vascular disease versus prevalent vascular disease at 1 and ≥2 sites pretransplantation), all-cause mortality and death with a functioning graft, according to recipients of live-donor and deceased donor kidney transplants.

alter the clinical decision-making process in determining transplant suitability, it is conceivable that clinicians may have a disparate approach in establishing transplant suitability of patients with prevalent vascular disease (i.e. greater acceptance of higher risk transplants who otherwise would not be deemed suitable for deceased donor transplant wait-listing) because of the anticipated shorter waiting time, ability to facilitate planned live-donor transplant operations and avoiding the utilization of a limited supply of deceased donor kidneys. The lower "baseline" mortality rates of live-donor recipients without prevalent vascular disease combined with the likelihood of survival bias of deceased donor transplant recipients (i.e. those with prevalent vascular disease who did not survive the "waiting period" prior to deceased donor kidney transplants were not included in this study) are other potential reasons for the observed difference in the magnitude of mortality risk in recipients of dissimilar donor types. More detailed analysis of the recipients with prevalent vascular disease who had experienced premature deaths within the first few years post-live–donor kidney transplantation (compared to deceased donor transplants), including the severity and adequate management of the prevalent vascular disease pretransplant, management of vascular risk factors pre- and post-transplantation and the ongoing follow-up of the vascular disease burden post-transplant would greatly inform clinicians regarding the selection and the potential shortcomings in the management of these patients (e.g. inadequate management of the vascular risk factors), which may ultimately result in improvement in short- and long-term outcomes of these high vascular risk patients.

Cardiovascular disease and cancer remain the dominant causes of death following kidney transplantation, although the rate of CVD mortality has steadily declined over the last decade, paralleling the improvements in the management of CVD risk factors [11]. In kidney transplant recipients with prevalent vascular disease or vascular risk factors such as diabetes, an excess of CVD, infection, and other vascular disease-related mortality may explain the higher rates of death post-transplantation [6,16]. Similarly, the risk of CVD and infection-related mortality was up to three times greater in live-donor recipients with vascular disease compared to those without. The reason for the greater risk of infection-related mortality in patients with prevalent vascular disease is unclear and will require further investigations in future studies. These patients were also more likely to be diabetic which likely is contributing to the higher mortality rates. Patients with diabetes and PVD have a dampened immune system increasing the risk of infectious complications [17]. There are multiple potential mechanisms including alterations in both humoral and cellular mechanisms which may result in a higher infection-related mortality in patients with significant vascular disease burden.

Despite the fact that the overall allograft survival was significantly poorer for recipients with prevalent vascular diseases, the risk of death censored allograft failure was not influenced by the presence or burden of vascular disease, with the disparity in overall allograft survival between those with and without prevalent vascular disease explained by differences in the incidence of death with a functioning graft. This dichotomy between allograft and patient survival makes clinical selection of potential live-donor kidney transplant recipients challenging, with clinicians, patients and corresponding live-donors needing to balance the trade-offs in risks and benefits when considering live-donor kidney transplant in patients with prevalent vascular disease.

There are a number of strengths and limitations of our study that are noteworthy. The large sample size and extended duration of follow-up ensure the accuracy of capturing important clinical outcome. Nevertheless, selection bias is likely to exist because there may be systematic differences in considering live-donor transplantation of ESKD patients with and without prevalent vascular disease, as well as differences in the management of these recipients pre- and post-transplant. Even though multiple confounding factors were adjusted for, there are several other unmeasured and residual confounders such as the change in vascular disease burden over time, the severity and treatment of vascular disease (s), which are not collected by ANZDATA registry but may have modified the study findings. ANZDATA registry does not reliably capture *de novo* vascular disease but, as this can only occur in those without prevalent vascular disease at time of transplantation, the omission of this data would only serve to enhance the survival disadvantage between those with and without prevalent vascular disease. Recipients of live-donor kidney transplants in our study had a low prevalence of vascular disease and/or diabetes limiting the generalizability of our results. However, other registries have also shown a lower prevalence of comorbidities in recipients of live-donor kidney transplants compared to deceased donors [18].

Live-donor kidney transplantation leads to significantly better outcomes than deceased donor and thus is the treatment of choice for many patients with ESKD.

Despite these benefits, vascular disease burden negatively impacts patient outcomes. This information should be integral in the shared decision-making between clinician and patient when discussing options of transplantation. Potential live-donors consenting for nephrectomy must also be informed of the expected outcomes in their intended recipients. It would not be appropriate to deny live-donor kidney transplantation for these recipients, but rather inform our patients and their physicians of potential risks and highlight the importance of aggressive cardiovascular risk factor reduction. Further study is still required to dissect the characteristics and management of patients who suffer early mortality.

Authorship

All authors substantially contributed to conception and design, and acquisition of data or analysis, interpretation of data, drafting the article and gave final approval of the version to be published.

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SUPPORTING INFORMATION

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

Figure S1. Study population flow chart.

Figure S2. Adjusted cumulative incidence function curves of cardiovascular disease (CVD)-related mortality (a) and infection-related mortality (b) after live-donor kidney transplantation stratified by vascular disease burden (i.e. no prevalent vascular disease versus prevalent vascular disease at 1 and ≥2 sites pretransplantation), adjusted for the competing risk of non-CVD and non-infection-related mortality, respectively.

Table S1. STROBE Statement checklist of items.

Table S2. Baseline characteristic of live and deceased donor kidney transplant recipients between 1980 and 2014.

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