Factors Influencing Long-Term Patient and Allograft Outcomes in Elderly Kidney Transplant Recipients

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Introduction: Individuals aged ≥65 years are increasingly prevalent on the waitlist for kidney transplantation, yet evidence on recipient and donor factors that define optimal outcomes in elderly patients after kidney transplantation is scarce.

Methods: We used multivariable Cox regression modeling to determine the factors associated with all-cause death, death with a functioning graft, and overall and death-censored graft survival, using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry.

Results: A total of 802 kidney transplant recipients aged ≥65 years underwent their first transplantation between June 2006 and December 2016. Median age at transplantation was 68 years (interquartile range = 66−69 years). The 1-year and 5-year overall patient and graft survivals (95% confidence interval [CI]) were 95.1 (93.5−96.7) and 79.0 (75.1−82.9), and 92.9 (91.1−94.7) and 75.4 (71.3−79.5), respectively. Factors associated with higher risks of all-cause death included prevalent coronary artery disease (adjusted hazard ratio [95% confidence interval] = 1.47 [1.03–2.11]), cerebrovascular disease (1.99 [1.26–3.16]), increasing graft ischemic time (1.06 per hour [1.03–1.09]), donor age (1.02 per year [1.01–1.03]), delayed graft function (1.64 [1.13−2.39]), and peritoneal dialysis pretransplantation (1.71 [1.17−2.51]).

Conclusion: Prevalent vascular disease and peritoneal dialysis as a pretransplantation dialysis modality are risk factors associated with poorer outcomes in transplant recipients aged ≥65 years. Careful selection and evaluation of potential candidates may improve graft and patient outcomes in older patients.

ndividuals aged ≥65 years have the highest incidence of kidney failure commencing kidney replacement therapy (KRT) in most high-income countries.[1] In Australia, the 2 age groups with the highest incidence of commencement of KRT are those aged 75 to 84 years (491 per million population [pmp]) and those aged 65 to 69 years (391 pmp).[2] Similar trends are also observed worldwide. In the United States, the age group with the highest incidence rate of treated end-stage kidney disease are those aged 75 years and over (1360 pmp) and those aged 65 to 74 years (1156 pmp), compared to 550 pmp for younger patients aged 45 to 64 years.[3] In Europe, approximately 56% of all incident patients commencing KRT are aged >65 years.[4] Kidney transplantation is a practical option for older patients on dialysis. There is now indisputable evidence from observational studies suggesting that kidney transplantation improves the quality of life and survival for most patients with kidney failure, even in elderly individuals.[5−7] Chronological age is no longer a contraindication for kidney transplantation because of the incremental gains in life-years and quality-adjusted life-years experienced by older patients with functioning grafts compared to maintenance dialysis.[8]

Elderly candidates represent an increasingly prevalent group on the waitlist for kidney transplantation. However, age-related comorbidities such as ischemic heart disease, peripheral vascular disease, and frailty are risk factors for premature death and postoperative complications after transplantation.[9−13] The risk of

early postoperative death is also high among recipients aged ≥65 years, with an increased risk of death by 1.5 times during the perioperative period compared to those remaining on dialysis.[6,7]

Careful selection of suitable candidates is therefore central to attenuate the risk of postoperative complications and to ensure appropriate utilisation of the precious resources. Yet knowledge of recipient- and donor-related factors that contribute to optimal outcomes in older recipients after kidney transplantation are unclear, because most studies that have included patients aged ≥65 years are limited by small sample size, without relevant listing data and hence with uncertain effects on patient-relevant outcomes.[14−16] In this study, we aimed to determine the recipient-related and donor-related factors that are associated with patient and graft survivals in a large cohort of kidney transplant recipients aged ≥65 years.

MATERIALS AND METHODS

Study Population

This observational study used linked data between the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry and the National Organ Matching System (NOMS). Data were collected through the calendar year by medical and nursing staff in each renal unit in Australia and New Zealand and submitted annually to the ANZDATA registry by the end of March in the following year. We included all Australian patients who had commenced dialysis when aged ≥65 years and were subsequently placed on the deceased donor kidney transplant waitlist between 28 June 2006 and 31 December 2016 (inclusive), who then received their first kidney transplant (living or deceased donor) during this study period. This study was approved by the Western Sydney Local Health District ethics committee. We adhered to the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for conduct and reporting (see Supplementary Material).

Data Collection

Baseline data on recipients included age, ethnicity, sex, Socio-Economic Indexes for Areas (SEIFA) score (with a higher score indicating greater socioeconomic advantage), causes of primary renal disease, and comorbidities (including coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus) at the time of waitlisting and transplantation, and smoking status (at the time of renal replacement therapy). We also collected data on the date and cause of death. Transplantation data collected included the date of the kidney transplantation, donor details (age, sex, and total ischemic time in hours), data

on immediate graft function (with "delayed graft function" defined as "no immediate function and dialysis required within 72 hours" and with "no delayed graft function" defined as "spontaneous fall in serum creatinine by 10% within 24 hours", "spontaneous fall in serum creatinine by 10% first recorded between 25 and 72 hours", or "poor immediate function with no spontaneous fall in serum creatinine within 72 hours but no dialysis required"), and date and cause of graft failure. Data collected from NOMS included dates of waitlisting and waitlisting status for each recipient.

Outcomes

The primary outcome was overall patient survival, defined as time from kidney transplantation to death, censored for loss to follow-up or end of inclusion period for the study (31 December 2016).

Secondary outcomes included death with a functioning graft (censored for graft failure, loss to follow-up, or end of the inclusion period), overall graft survival (censored for loss to follow-up and end of the inclusion period), and death-censored graft survival (censored for death, loss to follow-up, or end of the inclusion period). Overall graft survival was defined as the time from kidney transplantation until death with a functioning graft or return to dialysis.

Covariates

Recipient factors that were analyzed as potential risk factors were sex, age at transplantation, Socioeconomic Index for Area (SEIFA) score, primary renal disease, dialysis modality at time of transplantation (hemodialysis [HD], or peritoneal dialysis [PD]), ethnicity (Caucasian, Aboriginal/Torres Strait Islander, Asian, Maori, Pacific and other), smoking status, comorbidities at time of transplantation (coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, diabetes mellitus), body mass index at time of transplantation (kg/m^2), state of residence at time of transplantation, year of transplantation, acute rejection (defined by ANZDATA as rejection within the first 6 months posttransplantation), delayed graft function (which we defined as "no immediate function and dialysis required within 72 hours" from the data available from the ANZDATA Registry), and time on dialysis prior to transplantation. The total time that a patient was not active on the deceased donor waitlist was calculated as a proportion of the total time from time of being waitlisted to transplantation. Donor-related factors that were also assessed as potential risk factors included the age of the donor, sex, deceased versus living kidney donor status, and ischemic time.
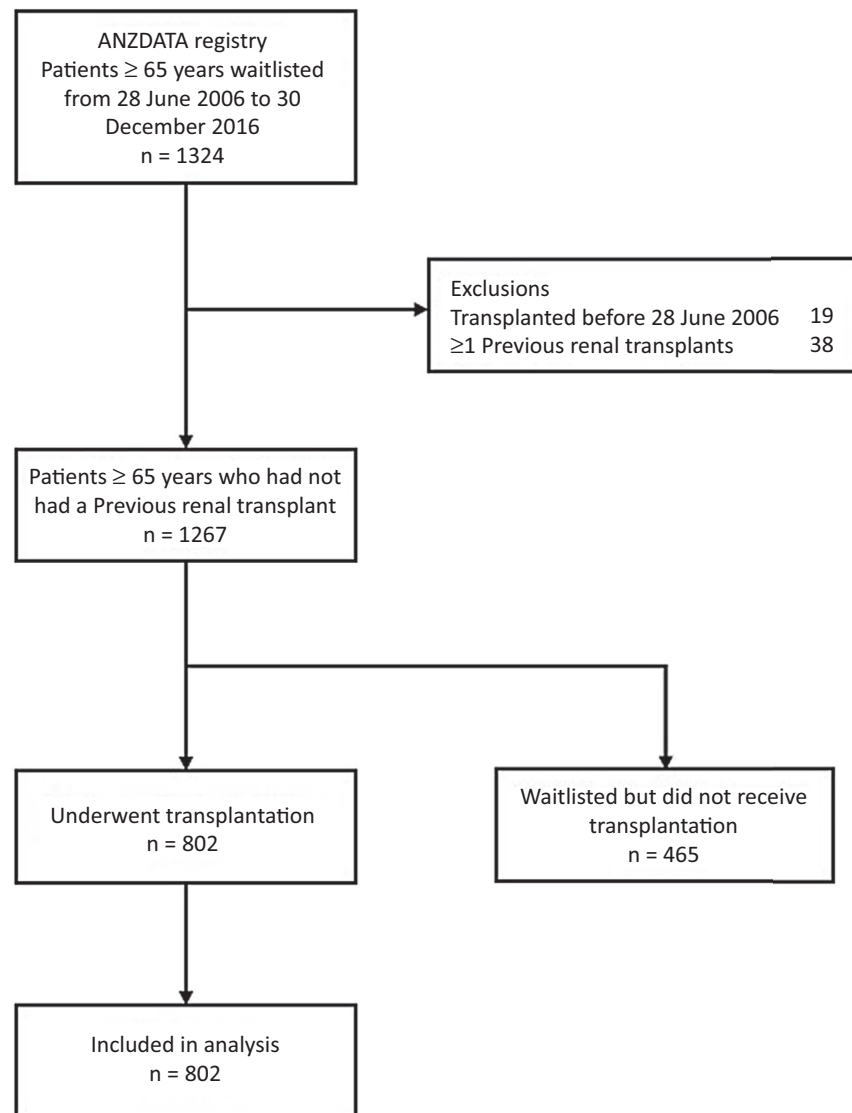
Figure 1. Patient flow throughout the study. ANZDATA, Australia and New Zealand Dialysis and Transplant.

Statistical Analyses

Continuous variables were summarized using means and SDs for normally distributed variables, and medians and interquartile ranges for non—normally distributed variables. Comparison of baseline characteristics between recipients who reached the primary outcome of interest (i.e., death) and those who did not, were made by the Student t test and χ^2 test for continuous and categorical variables, respectively.

Cox proportional hazard models were used to assess predictors of all-cause mortality, death with a functioning graft, and overall and death-censored graft loss. Kaplan—Meier curves were constructed to estimate survival time until all-cause mortality, death with a functioning graft, and overall and death-censored graft loss. Sensitivity analyses were performed using Fine and Gray competing risks models[17] for graft failure, with death as a competing event, and death with graft failure as a competing event.

For each model, potential risk factors were first assessed by univariable analysis. Variables with P values <0.20 on univariable analysis were included in the initial multivariable model. Backward stepwise variable selection was applied, and variables with P values <0.05 in the multivariable model were kept. Acute rejection was modeled as a time-dependent covariate, with time without a prior rejection episode considered "no previous rejection" and time after experiencing any acute rejection episode counted as "rejection." We performed prespecified tests for effect modification between patient age at transplantation and sex and the other included covariates in the models. Statistical analyses were performed with IBM SPSS Statistics v22.0 (IBM Corporation, Armonk, NY) and R version 3.6.0 (R Foundation, Vienna, Austria). A P value of ʿ0.05 was regarded as significant. The proportional hazard assumption was assessed in all models using the *coxph.zph* function and graphically by

Table 1. Baseline characteristics of patients who received their first kidney transplant

Overall cohort		N = 802
Male sex, n (%)		531 (66.2%)
Age, yr, mean ± SD	Age first active on waitlist >65	67.02 ± 3.3
	Age at commencement of renal replacement therapy	67.1 ± 2.7
SEIFA (mean ± SD)	SEIFA at time of first waitlist	996.6 ± 70.7
	SEIFA at transplantation	996.1 ± 69.4
Year of transplantation, n (%)	2006 – 2010	292 (36.4%)
	2011 – 2016	510 (63.6%)
Comorbidities at renal replacement therapy	Current or former smoker, n (%)	393 (49%)
Comorbidities at transplantation (n, %)	Chronic lung disease presented or suspected	108 (13.5%)
	Coronary artery disease present or suspected	302 (37.7%)
	Peripheral vascular disease present or suspected	153 (19.1%)
	Cerebrovascular disease present or suspected	91 (11.4%)
	Diabetes mellitus type 1 or 2 present	299 (37.3%)
	BMI, mean ± SD	27.5 ± 4.7 kg/m²
Racial origin, n (%)	Caucasian	674 (84%)
	Asian	76 (9.5%)
	Aboriginal/Torres Strait Islander	14 (1.6%)
	Pacific	6 (0.7%)
	Maori	6 (0.7%)
	Other or unknown	27 (3.4%)
Birth country, n (%)	Australia or New Zealand	469 (57.5%)
	Other or unknown	333 (42.5%)
Primary renal disease, n (%)	Glomerulonephritides	276 (34.4%)
	Diabetes mellitus	147 (18.3%)
	Polycystic kidney disease	118 (14.7%)
	Renovascular disease	107 (13.3%)
	Unknown	41 (5.1%)
	Reflux nephropathy	27 (3.4%)
	Toxins (e.g., cadmium, lithium, analgesic nephropathy)	23 (2.9%)
	Obstructive uropathy	17 (2.1%)
	Interstitial nephritis	14 (1.7%)
	Congenital reasons	12 (1.5%)
	Shock (e.g., septic or cortical necrosis)	7 (0.9%)
	Malignancy	6 (0.7%)
	Amyloidosis or light chain nephropathy	2 (0.6%)
	Other	5 (0.6%)
Renal replacement therapy at transplantation, n (%)	Hemodialysis	573 (71.4%)
	Peritoneal dialysis	226 (28.2%)

BMI, body mass index; SEIFA, Socio-Economic Indexes for Areas.

plotting Schoenfeld residuals. No evidence of departure from the proportional hazards assumption was found in all models.

RESULTS

Characteristics of the Study Cohort

A total of 1324 patients commenced KRT aged ≥65 years and were listed on the deceased donor kidney transplant waitlist between June 2006 and December 2016. Of these, 1267 had no prior transplants. In all, 802 received either a deceased or living donor transplant during this period (Figure 1).

Most transplant recipients were men (531, 66.2%). Seven hundred five (87.9%) recipients received transplants from deceased donors. The median age at transplantation was 68 years (interquartile range

[IQR]: 66−69 years). The median time on renal replacement therapy was 37.9 months. The median time from kidney replacement therapy to waitlisting was 16.6 months (IQR: 8.7−31.7 months). The most common causes of primary kidney disease were glomerulonephritis (n = 276, 34.4%), followed by diabetes mellitus types 1 and 2 (n = 147, 18.3%) and polycystic kidney disease (n = 118, 14.7%). Median ischemic time was 11 hours (IQR = 7−15 hours). Baseline characteristics of patients who received their first kidney transplants are shown in Table 1.

Patient Survival

Over a follow-up time of 2707 patient-years, 136 patients (17% of total patients) died, and 111 patients (81.6% of total deaths) died with a functioning graft. The 1-year and 5-year overall patient survivals post-
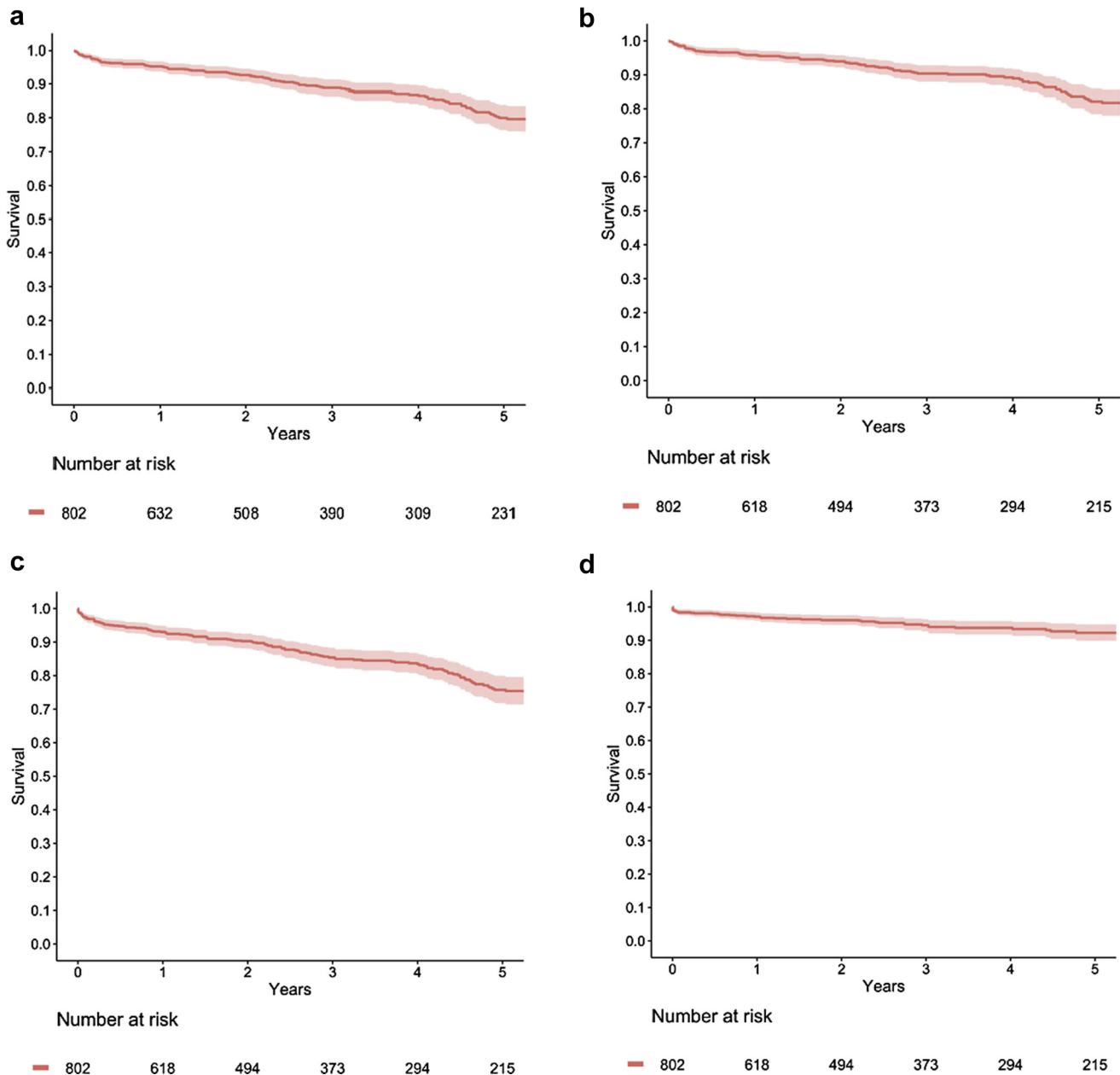
Figure 2. (a) Kaplan−Meier estimates of the 5-year overall patient survival of kidney transplant recipients. (b) Kaplan−Meier estimates of the 5-year patient survival with functioning graft among kidney transplant recipients. (c) Overall graft survival of kidney transplant recipients. (d) Death-censored graft survival.

transplantation were 95.1% (95% CI = 93.5%−96.7%) and 79% (95% CI = 75.1%−82.9%) respectively (Figure 2a). The 1-year and 5-year survivals with a functioning graft were 95.7% (95% CI = 94.3%−97.1%) and 82.4% (95% CI = 78.8%−86.1%) (Figure 2b).

Causes of death are shown in Figure 3.

Factors Associated With All-Cause Death and Death With a Functioning Graft

Factors associated with all-cause death (adjusted HR [95% confidence interval]) included pretransplantation dialysis modality as peritoneal dialysis (1.71 [1.17−2.51]), prevalent coronary artery disease (1.47 [1.03−2.11]), prevalent cerebrovascular disease (1.99 [1.26−3.16]), total ischemic time (1.06 per hour [1.03−1.09]), increasing donor age (1.02 per year [1.01−1.03]), and delayed graft function (1.64 [1.13−2.39]). Factors associated with all-cause death and death with a functioning graft (discussed below) are represented in Figure 4.

Factors associated with death with a functioning graft (adjusted HR [95%] were pretransplantation dialysis modality (PD) (1.70 [1.13−2.55], $P = 0.01$), prevalent coronary artery disease (1.59 [1.08−2.35] $P = 0.02$), increasing donor age (1.02 per year increase
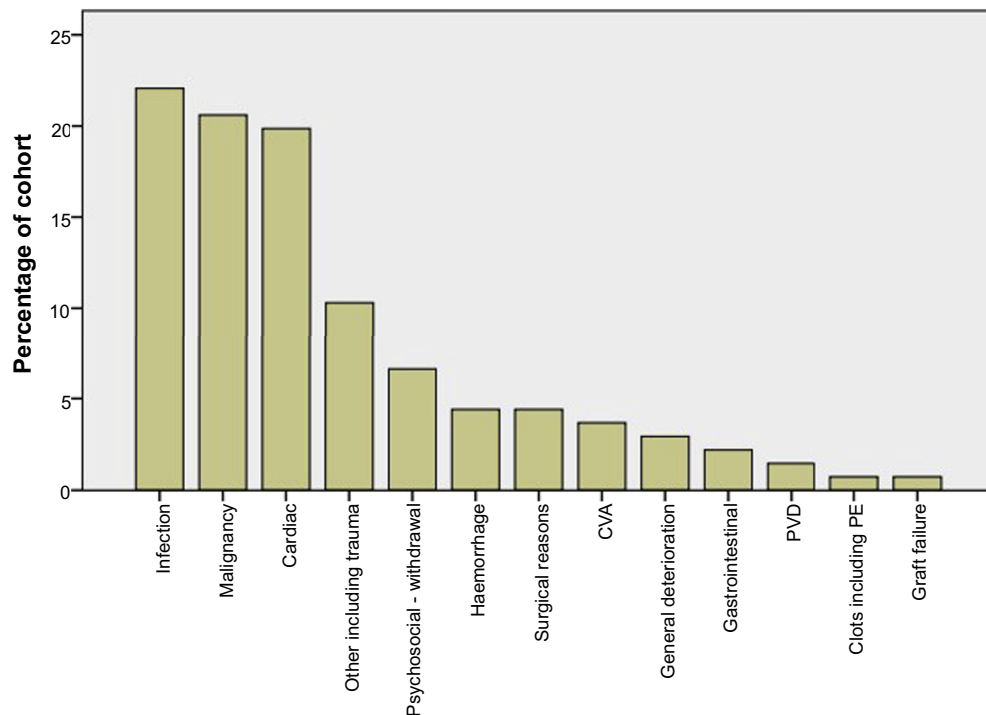
Figure 3. Causes of death in patients who received a kidney transplant. CVA, cerebrovascular accident; PE, pulmonary emboli; PVD, peripheral vascular disease.

[1.00–1.03], $P = 0.02$), and increasing ischemic time (1.05 per 1-hour increase [1.02–1.09], $P = 0.004$). In the sensitivity analysis, similar estimates were found for the association between death and pre-transplantation dialysis modality (PD) (1.69 [1.14–2.50], $P = 0.009$), coronary artery disease at time of transplantation (1.58 [1.08–2.31], $P = 0.02$), and increasing graft ischemic time (1.05 per hour increase [1.02–1.08], $P = 0.004$), in the competing risk model (with graft loss considered as a competing risk event) (Supplementary Table S4).

Graft Survival
Overall, 51 patients (6.4%) lost their allografts. Causes of graft loss are shown in Figure 5. The 1-year and 5-year overall graft survivals were 92.9% (95% CI =

91.1%−94.7%) and 75.4% (95% CI = 71.3%−79.5%) (Figure 2c), respectively. The 1-year and 5-year death-censored graft survivals were 96.8% (95% CI = 95.4%−98.2%) and 92% (95% CI = 89.8%−94.2%) (Figure 2d).

Factors Associated With Overall Graft Survival and Death-Censored Graft Loss
Factors associated with lower overall graft survival (adjusted HR [95% CI]) were cerebrovascular disease (1.70 [1.10–2.63], $P = 0.02$), increasing ischemic time (1.04 per hour increase [1.01–1.07], $P = 0.01$), increasing donor age (1.02 per year increase [1.01–1.03], $P < 0.001$), acute rejection (1.54 [1.04–2.26], $P = 0.03$), and delayed graft function (1.59 [1.14–2.24], $P = 0.007$). Factors associated with death-censored graft loss
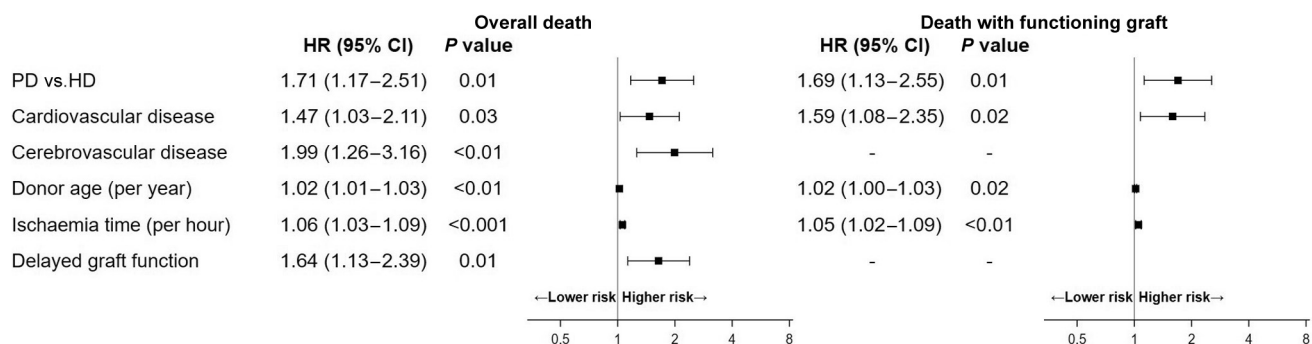
	Overall death			Death with functioning graft		
	HR (95% CI)	P value		HR (95% CI)	P value	
PD vs.HD	1.71 (1.17–2.51)	0.01		1.69 (1.13–2.55)	0.01	
Cardiovascular disease	1.47 (1.03–2.11)	0.03		1.59 (1.08–2.35)	0.02	
Cerebrovascular disease	1.99 (1.26–3.16)	<0.01		-	-	
Donor age (per year)	1.02 (1.01–1.03)	<0.01		1.02 (1.00–1.03)	0.02	
Ischaemia time (per hour)	1.06 (1.03–1.09)	<0.001		1.05 (1.02–1.09)	<0.01	
Delayed graft function	1.64 (1.13–2.39)	0.01		-	-	

←Lower risk Higher risk→   ←Lower risk Higher risk→

Figure 4. Factors associated with all-cause death and death with a functioning graft. CI, confidence interval; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis.
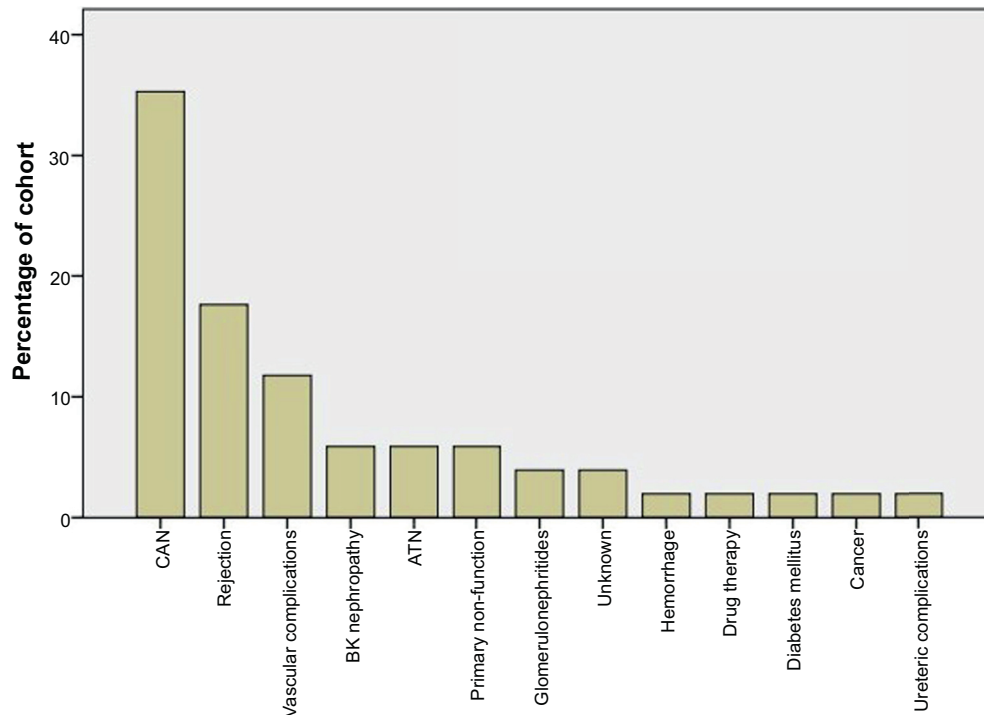
Figure 5. Causes of graft failure in kidney transplant recipients. ATN, acute tubular necrosis; CAN, chronic allograft nephropathy.

(adjusted HR [95% CI]) were cerebrovascular disease (2.44 [1.20−4.95], *P* = 0.01], acute rejection (4.27 [2.28−7.98], *P* = 0.01), increasing donor age (1.04 per year increase [1.01−1.06], *P* = 0.002) and delayed graft function (2.92 [1.63−5.25], *P* < 0.001). Recent transplant era was associated with improved graft survival (0.85 per year increase [95% CI = 0.76−0.96], *P* = 0.009). Factors associated with overall graft survival and death-censored graft loss are shown in Figure 6.

In the sensitivity analysis, similar estimates were found for the association between cerebrovascular disease (2.32 [1.10−4.88], *P* = 0.03), acute rejection episodes (4.29 [2.18−8.44], *P* = 0.02), increasing donor age (1.03 per year increase [1.01−1.06], *P* = 0.008), and delayed graft function (2.73 [1.49−5.01], *P* = 0.001) with graft survival in the competing risk model (with death considered a competing risk event). Recent

transplant era was found to be associated with improved graft survival (0.84 [0.74−0.94], *P* = 0.003) (Supplementary Tables S6 and S7).

Increasing proportion of inactive time on the waitlist was not associated with adverse patient and graft outcomes after transplantation (adjusted HR [95% CI] = 1.51 [0.89–2.55] and 1.01 [0.62–1.64], respectively). Donor type (living vs. deceased donor) was not associated with overall patient and graft survival (*P* = 0.61 and *P* = 0.63, respectively).

For patients who were on hemodialysis prior to transplantation, the median time from KRT to waitlisting was 18.4 months (IQR = 9.7–37.4 months), and median time on KRT prior to transplantation was 42.1 months (IQR = 23.9–64.5 months).

In comparison, patients on peritoneal dialysis prior to transplantation had a median time from KRT to
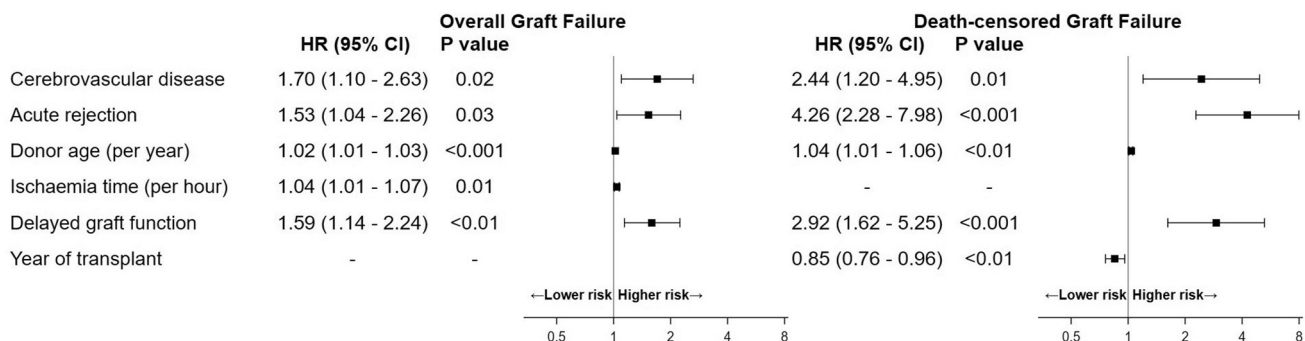

Figure 6. Factors associated with overall graft survival and death-censored graft loss.

waitlisting of 13.0 months (IQR = 7.0–4.0 months) and median time on KRT prior to transplantation of 29.6 months (IQR = 17.2–48.9 months).

DISCUSSION

In this selected cohort of elderly transplant recipients, our study findings suggest that overall patient and graft survival rates may be comparable to those in younger recipients, with 5-year patient and death-censored graft survivals exceeding 75%. These patient and graft survivals are higher than what has been previously reported in older transplant recipients (aged ≥65 years). Such discrepant findings may be attributed to the younger donor ages observed in our study and also recipients from different transplantation eras. A single prior study has focused on recipients who received their first transplant largely in the last decade (2002–2012).[18] Apart from the known recipient-related risk factors for death including coronary artery disease and cerebrovascular disease,[14,19] we have shown that dialysis modality prior to transplantation is a risk factor for adverse outcomes after transplantation. Patients on peritoneal dialysis prior to transplantation experienced an excess risk of death by 1.5-fold compared to patients on maintenance hemodialysis.

On the contrary, prior work indicated pretransplant dialysis modality was not a risk factor for patient survival.[19–26] However, most of the published data included younger populations, with a mean age of recipients under 50 years.[19,20,26] Given the observational nature of the analyses, participants were not randomly assigned to the initial type of dialysis. Inherent biases including selection, confounding, and indication biases may exist; therefore, causality cannot be established. Patients on PD typically have lower hemoglobin and serum albumin levels compared to patients with pretransplantation HD,[20] and this may have contributed to the increased risk of death. Consistent with previous literature,[27] in our cohort, those patients on HD had a higher prevalence of coronary artery disease (Supplementary Material). However, 1 recent paper[27] showed that despite this higher prevalence, there was no difference in survival between patients receiving HD and those receiving PD, but there was a trend toward increased mortality in those aged ≥65 years who were receiving PD with a dialysis vintage of over 3 years. This is also applicable to many of the patients on PD prior to transplantation in our cohort, who had a mean dialysis vintage of more than 3 years, and may partly explain our finding. Further investigation into the role of dialysis-related factors and its impact on elderly kidney transplant recipients is warranted.

Although preferential allocation of older donors to older recipients is not an explicit criteria for the deceased donor organ allocation in Australia, as is currently implemented in the Eurotransplant Program[28] and the US Kidney Allocation System,[28] there is evidence to suggest that an "old-for-old" standard has been applied implicitly in the Australian deceased donor allocation system. Given the persistent shortage of donor organs and the advancing age of the end-stage kidney disease population, balancing utility (allocation of organs to those who derive the greatest benefit) against justice (equal access to transplantation for all age groups) is a critical element for consideration of an equitable deceased donor allocation algorithm within Australia.[29] Transplantation of an elderly recipient with an older kidney still offers a survival benefit over dialysis,[6] and reduces waiting time for transplantation,[30] but these advantages need to be carefully weighed against the known risk of increased graft loss and mortality compared to those in recipients of deceased donor kidneys with higher kidney donor profile index (KDPI).[30]

The most common cause of death in our study was infectious complications, which is consistent with prior literature in the elderly kidney transplantation population.[31–33] A single study suggested that reduction of immunosuppression in elderly patients aged ≥60 years[34] was associated with improved patient and graft outcomes, but current guidelines do not consider the adverse effects such as catastrophic infections that are unique and important to older recipients.[35] Evidence on recommended immunosuppressive regimens is derived mainly from trials in which where elderly patients were either excluded or a minority.[36] Any reduction of immunosuppression must balance the risks and implications of increased rejection. Rejection episodes in the elderly transplant recipient may have a disproportionately higher adverse impact on graft loss compared to that in younger recipients.[37] Further comparative studies on the optimal immunosuppression regimen in this population is warranted.

One of the strengths of this study was the large and complete cohort, which included all elderly kidney transplant recipients in Australia and New Zealand during the study period, with few missing values, good follow-up data points, and involvement in all transplantation centers, thus enhancing external validity. However, our study has focused on a highly selected cohort of elderly patients, and these findings may not be generalizable to all patients of this age group on maintenance dialysis.

Our study also has several limitations. Residual confounding effects may exist, as details pertaining to

the parameters of dialysis adequacy prior to transplantation and the reasons for the choice of pretransplantation dialysis modality were not collected routinely. Furthermore, frailty is a risk factor for poor outcomes posttransplantation,[9] and markers of frailty are not routinely collected by the registry. Other information such as the severity of disease are not routinely collected, and prior treatment or interventions of vascular comorbidities are also not reported within the registry. Similarly, details regarding the stage and histological types of prior cancers were also missing. As such, we were unable to quantify the impact of these co-existing comorbidities as potential prognostic factors on death.

Although the relative risk of mortality is increased in the elderly transplant recipient compared to younger transplant recipients,[38] it is reassuring to note that the absolute rates of death 1 year and 5 years posttransplantation among older recipients remains low. Pre-existing vascular disease is a major risk factor for adverse outcomes after transplantation, and careful evaluation and selection of the appropriate candidates is necessary to ensure optimal patient outcomes and use of this scarce resource.

In conclusion, in this selected cohort of elderly kidney transplant recipients, 5-year patient and graft survivals exceeded 75%. Results from this study have identified several factors associated with death and graft failure, which may be critical to inform the selection and to identify targets of opportunity to improve outcomes in elderly dialysis patients for future kidney transplantation.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualisation and design of the study. SS was involved in data acquisition, cleaning, analysis, literature review, and drafting the manuscript. SS and EA were involved in data analysis. All authors reviewed the results and revised the manuscript for intellectual content. All authors provided final approval for the version to be published and are accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Checklist

Table S1. Comparison of baseline characteristics between patients who reached the primary outcome of interest, death, and those who did not

Table S2. Univariable analyses for outcome: death

Table S3. Univariable analyses for outcome: death with a functioning graft

Table S4. Univariable analyses for outcome: death (competing risk model)

Table S5. Univariable analyses for outcome: overall graft failure

Table S6. Univariable analyses for outcome: death-censored graft failure

Table S7. Univariable analyses for outcome: graft failure (competing risk model)

Table S8. Comparison of baseline characteristics between patients receiving hemodialysis and peritoneal dialysis at time of transplantation

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