Article

Infection-Related Mortality in Recipients of a Kidney Transplant in Australia and New Zealand

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Abstract

Background and objectives The burden of infectious disease is high among kidney transplant recipients because of concomitant immunosuppression. In this study the incidence of infectious-related mortality and associated factors were evaluated.

Design, setting, participants, & measurements In this registry-based retrospective, longitudinal cohort study, recipients of a first kidney transplant in Australia and New Zealand between 1997 and 2015 were included. Cumulative incidence of infectious-related mortality was estimated using competing risk regression (using noninfectious mortality as a competing risk event), and compared with age-matched, populated-based data using standardized incidence ratios.

Results Among 12,519 patients, (median age 46 years, 63% men, 15% diabetic, 6% Indigenous ethnicity), 2197 (18%) died, of whom 416 (19%) died from infection. The incidence of infection-related mortality during the study period (1997–2015) was 45.8 (95% confidence interval [95% CI], 41.6 to 50.4) per 10,000 patient-years. The incidence of infection-related mortality reduced from 53.1 (95% CI, 45.0 to 62.5) per 10,000 person-years in 1997–2000 to 43.9 (95% CI, 32.5 to 59.1) per 10,000 person-years in 2011–2015 ($P<0.001$) Compared with the age-matched general population, kidney transplant recipients had a markedly higher risk of infectious-related death (standardized incidence ratio, 7.8; 95% CI, 7.1 to 8.6). Infectious mortality was associated with older age ($\geq$60 years adjusted subdistribution hazard ratio [SHR], 4.16; 95% CI, 2.15 to 8.05; reference 20–30 years), female sex (SHR, 1.62; 95% CI, 1.19 to 2.29), Indigenous ethnicity (SHR, 2.87; 95% CI, 1.84 to 4.46; reference white), earlier transplant era (2011–2015: SHR, 0.39; 95% CI, 0.20 to 0.76; reference 1997–2000), and use of T cell–depleting therapy (SHR, 2.43; 95% CI, 1.36 to 4.33). Live donor transplantation was associated with lower risk of infection-related mortality (SHR, 0.53; 95% CI, 0.37 to 0.76).

Conclusions Infection-related mortality in kidney transplant recipients is significantly higher than the general population, but has reduced over time. Risk factors include older age, female sex, Indigenous ethnicity, T cell–depleting therapy, and deceased donor transplantation.

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Introduction

A major challenge in kidney transplantation is the management of infectious complications, which causes substantial morbidity and mortality in this vulnerable population (1–3). With the lower risks of rejection over time, short- and longer-term infection and malignancy complications represent a greater relative challenge. Worldwide, the incidence of infectious complications among recipients of a kidney transplant has been reported to range from 49% to 80% (4,5). Consistent with disease burden, the Standardized Outcomes of Nephrology Group in Transplantation has identified infection as a core outcome that is critically important to clinicians, patients, and their caregivers (6).

However, despite being a priority outcome, evaluation of the incidence and factors associated with infectious mortality after kidney transplantation is scarce. Recently, a Finnish Registry study of 3249 adult first kidney transplant recipients between 1990 and 2012 reported that infection accounted for 21% of all deaths, mostly (89%) occurring after the first year, and were associated with older recipient age, diabetic kidney disease, longer pretransplant dialysis duration, acute rejection, and a higher serum creatinine concentration at 1 year after transplantation (7). Another key finding of this investigation was that the incidence of infectious mortality fell markedly during the study period, with infectious death in the most recent cohort (2000–2012) being half that of the earlier

cohort (1990–1999) (7). In other studies, data from the United Kingdom Renal Registry have shown that infection-related mortality after kidney transplantation has remained stable at approximately 18% of all mortality between 2000 and 2011 (8,9), despite the fact that the proportion of cardiovascular deaths has progressively fallen from 34% in 2000 to 22% in 2011. Furthermore, a single-center Spanish study reported that among 1218 kidney transplant recipients analyzed between 1995 and 2004, most deaths were bacterial-related and the incidence of infection-related mortality had remained stable during this time (10).

Table 1. Characteristics of all first graft kidney transplant patients in Australia and New Zealand 1997–2015

Characteristics	Total Population (n=12,519)	1997–2005 (n=4838)	2006–2015 (n=7681)
Recipient characteristics			
Age (yr)			
<20	193 (2%)	96 (2%)	97 (1%)
20–29	1559 (12%)	763 (16%)	796 (10%)
30–39	2361 (19%)	1037 (21%)	1324 (17%)
40–49	3250 (26%)	1341 (28%)	1909 (25%)
50–59	3381 (25%)	1137 (23%)	2244 (29%)
≥60	1775 (14%)	474 (10%)	1301 (17%)
Sex			
Men	7827 (63%)	2948 (61%)	4879 (64%)
Ethnicity			
White	10,032 (80%)	4023 (83%)	6009 (79%)
Indigenous	696 (6%)	283 (6%)	429 (6%)
Asian	1138 (9%)	362 (7%)	776 (10%)
Other	653 (5%)	176 (4%)	405 (5%)
Country			
Australia	10,715 (86%)	4045 (84%)	6670 (87%)
New Zealand	1804 (14%)	795 (16%)	1009 (13%)
BMI categories (kg/m^2)			
<18.5	433 (4%)	189 (4%)	244 (3%)
18.5–24	5253 (42%)	2358 (49%)	2895 (38%)
25–29	4191 (34%)	1583 (33%)	2608 (34%)
30–34	1812 (14%)	512 (11%)	1300 (17%)
35–39	541 (4%)	132 (3%)	409 (5%)
≥40	289 (2%)	74 (1%)	215 (3%)
End-stage kidney failure cause			
Glomerulonephritis	5490 (44%)	2334 (48%)	3156 (41%)
Cystic kidney disease	1819 (15%)	623 (13%)	1196 (16%)
Reflux nephropathy	1000 (8%)	462 (10%)	538 (7%)
Renovascular	692 (5%)	184 (4%)	508 (7%)
Diabetic kidney disease	1866 (15%)	618 (13%)	1248 (16%)
Other	1652 (13%)	627 (13%)	1025 (13%)
Comorbidities (known or suspected)			
Chronic lung disease	822 (7%)	251 (5%)	571 (7%)
Coronary artery disease	1993 (16%)	579 (12%)	1414 (18%)
Peripheral vascular disease	1125 (9%)	363 (7%)	762 (10%)
Cerebrovascular disease	619 (5%)	197 (4%)	425 (6%)
Diabetes mellitus	2444 (20%)	766 (16%)	1678 (22%)
Donor characteristics			
Donor age (yr)			
<20	1028 (8%)	537 (11%)	491 (6%)
20–29	1294 (10%)	563 (12%)	731 (10%)
30–39	1652 (13%)	720 (15%)	932 (12%)
40–49	2833 (23%)	1176 (24%)	1657 (22%)
50–59	3203 (26%)	1185 (24%)	2018 (26%)
60–69	2047 (16%)	538 (11%)	1509 (20%)
≥70	462 (4%)	131 (3%)	331 (4%)
Donor source			
Deceased donor	8042 (64%)	3103 (64%)	4939 (64%)
Live donor	4477 (36%)	1737 (36%)	2740 (36%)
Transplant characteristics			
Baseline immunosuppression			
Tacrolimus/mycophenolate/prednisolone	7283 (60%)	843 (17%)	6440 (84%)
Cyclosporin/mycophenolate/prednisolone	4347 (35%)	2670 (55%)	1677 (22%)
Other	649 (5%)	97 (2%)	552 (11%)
Antirejection immunosuppression			
T cell–depleting therapy	982 (8%)	635 (36%)	347 (5%)

Missingness of baseline characteristics (<1%): body mass index, ethnicity, chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes (Supplemental Table 1).

In light of the possibility of regional and temporal variation in infection-related mortality, the aims of this study were to define the incidence of infection-related mortality among adult recipients of a first kidney transplant in Australia and New Zealand, to estimate the excess risk of infectious-related mortality compared with the general population, and to identify associated factors for infectious-related mortality to help better inform shared decision making by patients and clinicians.

Materials and Methods

Study Population and Setting

We conducted a retrospective, inception cohort study using patient records obtained from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. The ANZDATA Registry has collected data on all patients who commenced long-term kidney replacement therapy in all transplant units in Australia and New Zealand since 1963. Details regarding the structure and method of collection have been described previously (11). The study was conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines (12).

All adult (aged ≥18 years) patients with ESKD who underwent first kidney transplantation in Australia and New Zealand between January 1, 1997 and December 31, 2015 were included. Recipients undergoing subsequent kidney transplants and/or multiorgan transplants were excluded.

Data Collection

Data were collected on recipient characteristics (age, weight at time of transplant, height, self-reported ethnicity, country, sex, cause of ESKD, comorbidities [stroke, hypertension, peripheral vascular disease, diabetes, chronic lung disease]), donor characteristics (age, Kidney Donor Risk Index), transplant characteristics (date, maintenance immunosuppression regimen, antirejection therapy), and transplant outcomes (graft loss and all-cause and cause-specific death). Primary kidney disease was categorized as chronic GN, cystic kidney disease, reflux nephropathy, renovascular nephrosclerosis, diabetic kidney disease, and miscellaneous. Maintenance immunosuppressive therapy was divided into three groups: tacrolimus+mycophenolate+prednisolone, cyclosporine+mycophenolate+prednisolone, or other regimen. Other therapies included azathioprine, sirolimus, and clinical trial therapies (such as Pfizer drug JAK3, fingolimod, and sotrastaurin). T cell–depleting therapy, which was used as induction and for treatment, was also collected. The ANZDATA data collection form can be found at http://www.anzdata.org.au/forms/ANZDATA/ANZDATADialysisAndTransplantSurvey2017.pdf.

Outcomes

The primary outcome measure was time to mortality owing to infection with a functioning graft after kidney transplantation. Cause of death was judged and recorded by a clinician providing care to the patient. All causes of death were grouped into five categories: infection, cardiovascular disease, withdrawal from therapy, malignancy, or miscellaneous. A map of the different causes of death to these five categories is found in Supplemental Table 2. The causes of infectious deaths were further classified on the basis of organism (bacterial, viral, fungal, protozoal, other) and site of infection (pulmonary, septicemia, central nervous system, urinary tract, and other).

Statistical Analyses

Results were expressed as frequencies (percentages) for categorical data, mean±SD for continuous normally distributed data, or median (interquartile range) for continuous non-normally distributed data.

The incidence of infection-related mortality in the ANZDATA registry was compared with the incidence in the general population by comparing the number of infectious-related deaths and the person-years at risk for each group. Kidney transplant recipients were followed from the time of transplantation until death, loss to follow-up, or the end of study (December 31, 2015), whichever came first. General population event numbers and person-years at risk were derived from whole-population data provided by the Australian Institute of Health and Welfare (AIHW) (13). The AIHW publishes yearly data on the number of infectious deaths along with general population counts. The general population data were broken down into 5-year age groups. The ratios of the observed to the expected incidences of infectious mortality were calculated using the indirect age standardization method, and their 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution.

Multivariable competing risks regression was used to identify factors associated with time to infection-related mortality. Noninfectious deaths were considered as competing events. Patients were censored at the time of loss to follow-up, kidney transplant failure, or end of study (December 31, 2015). Variables with P values <0.2 in the
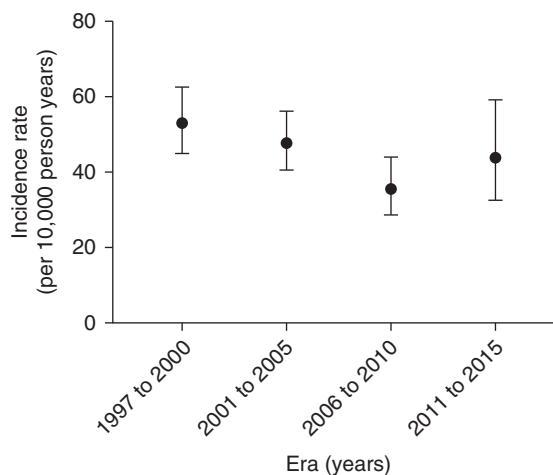

Figure 1. | Incidence of infection-related mortality by transplant era. Errors bars depict the lower and upper 95% confidence limits.
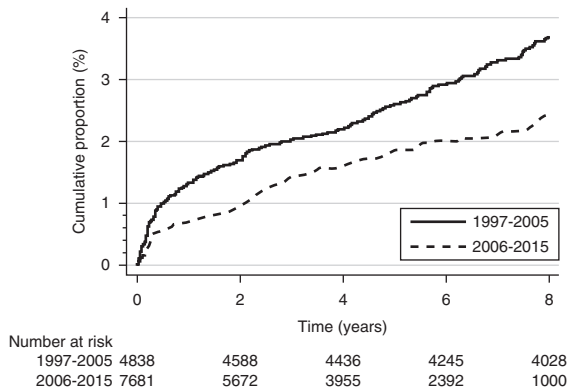
Figure 2. | **Cumulative incidence graph showing infection-related mortality by transplant era with competing risks of noninfectious mortality.**

univariable model were selected for the multivariable model. This was independent of their *P* value in the multivariable model or the effect of the variable on overall model selection criteria such as the Akaike information criterion. Interactions were tested for biologically-plausible effect modification by introducing a first-order multiplicative interaction term. Data were analyzed using Stata/SE version 14.0 (StataCorp, College Station, TX). *P* values <0.05 were considered statistically significant.

Results
Study Population
A total of 12,519 adults with ESKD who received their first kidney transplant in Australia and New Zealand were included (Table 1). During a median follow-up of 4.1 (interquartile range, 0.8–8.8) years, there were 2197 deaths. The causes of death were infection (*n*=416, 19%), cardiovascular (*n*=711, 32%), malignancy (*n*=492, 22%), withdrawal (*n*=258, 12%), and other causes (*n*=320, 15%). Twenty percent of deaths were attributable to infection, of which 75% were associated with a functioning graft.

Incidence of Infectious-Related Mortality
The overall incidence of infectious mortality during the study period (1997–2015) was 45.8 (95% CI, 41.6 to 50.4) per 10,000 patient-years. The incidence of infection-related mortality was 53.1 (95% CI, 45.0 to 62.5) per 10,000 person-years in 1997–2000, 47.8 (95% CI, 40.6 to 56.1) per 10,000 person-years in 2001–2005, 35.6 (95% CI, 28.7 to 44.1) per 10,000 person-years, and 43.9 (95% CI, 32.5 to 59.1) per 10,000 person-years in 2011–2015 ($P<0.001$) (Figure 1). The cumulative incidence of infection-related mortality by transplant era is shown in Figure 2.

Organism and Site-Specific Infectious Mortality
Bacterial infection accounted 223 (54%) infection-related deaths, fungi in 75 (18%), viruses in 34 (9%), protozoa in 15 (4%), and other organisms in 69 (16%). The median age at which patients died from an infection ranged between 49 and 52 years according to organism. Most patients who died from fungal and protozoal infections did so within the first 12 months after transplantation, whereas deaths from viral and bacterial infections occurred considerably later (Table 2). Deaths related to urosepsis occurred considerably later than deaths due to infection in other sites (Table 2). Supplemental Table 3 highlights the organism-specific mortality which occurred during the study period.

The incidence of organism-specific and site-specific mortality for the entire study period (1997–2015) is shown in Figure 3, A and B, respectively. The incidence of bacterial mortality was 32.5 (95% CI, 25.3 to 40.1) per 10,000 person-years in the 1997–2000 era and 18.4 (95% CI, 11.6 to 29.1) per 10,000 person-years in the 2011–2015 era ($P<0.001$). The incidence of fungal mortality increased from 6.4 (95% CI, 3.9 to 10.2) per 10,000 person-years in 1997–2000 to 17.3 (95% CI, 10.8 to 27.9) per 10,000 person-years in 2006–2015 ($P<0.001$). The incidence of pulmonary infection-related mortality reduced from 19.1 (95% CI, 14.5 to 25.1) per 10,000 person-years in 1997–2000 to 16.3 (95% CI, 10 to 26.6) per 10,000 person-years in 2011–2015 ($P<0.001$).

Given that follow-up durations differed significantly between different eras, the incidence of organism and

Table 2. **Organism and site-specific infectious death relative to median age at transplant and time after transplant**

| Characteristics	*n* (%)	Age at Transplant (yr), Median (IQR)	Time after Transplant (mo), Median (IQR)
Organism-specific death (*n*=416)			
Bacteria	223 (54)	51 (41–58)	64 (18–119)
Virus	34 (8)	54 (42–60)	30 (5–68)
Fungal	75 (18)	50 (41–60)	11 (3–41)
Protozoa	15 (4)	49 (45–57)	12 (4–81)
Miscellaneous	69 (16)	52 (42–57)	90 (30–126)
Site-specific death (*n*=416)			
Pulmonary	158 (38)	52 (43–60)	50 (9–104)
Septicemia	133 (32)	49 (38–58)	31 (4–91)
Central nervous system	30 (7)	51 (34–57)	28 (8–59)
Urinary tract	13 (3)	55 (47–62)	110 (42–134)
Miscellaneous	82 (20)	50 (42–58)	68 (26–128)

IQR, interquartile range.
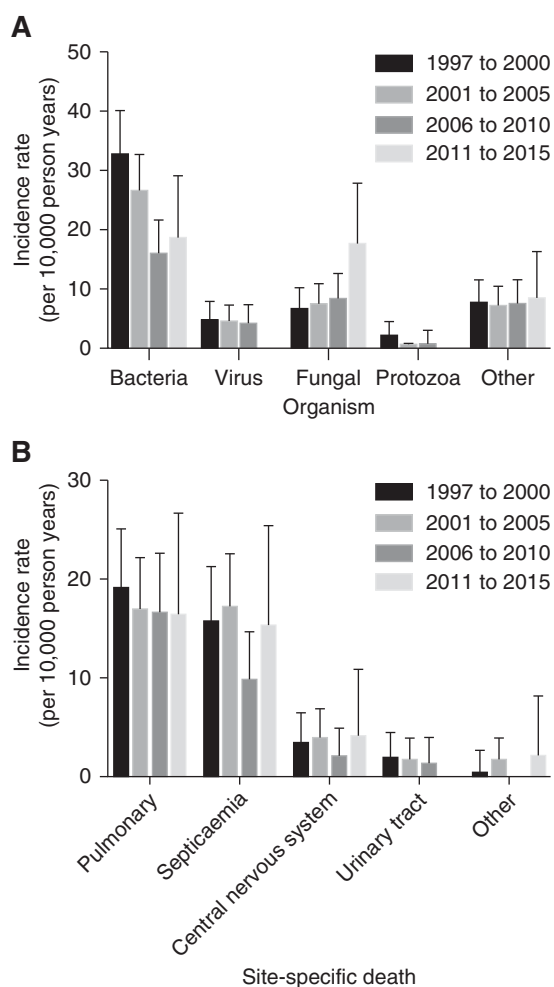
Figure 3. | **Incidence of infection-related mortality for study period (1997-2015) by transplant era.** (A) Incidence of organism-specific mortality for study period by transplant era. (B) Incidence of site-specific death for study period by transplant era. Errors bars depict the upper 95% confidence limits.

site-specific infectious mortality in the first 12 months after transplantation according to era were also ascertained, although this is limited by a small sample size and thus a wide confidence interval (Supplemental Figure 1, A and B).

Comparison with the General Population

Kidney transplant recipients were more likely to die from infection than the age- and sex-matched population

(standardized incidence ratio [SIR], 7.8; 95% CI, 7.1 to 8.6). This excess risk was more marked in women (SIR, 11.4; 95% CI, 9.8 to 13.1) than in men (SIR, 6.2; 95% CI, 5.5 to 7.1) (Table 3).

Factors associated with Infection-Related Mortality

The outcomes of univariable and multivariable competing risk methods model analyses are shown in Table 4. Older recipient age, female sex, Indigenous ethnicity, earlier transplant era, use of T cell–depleting therapy, and deceased donor kidney transplantation were associated with infectious mortality. There were no interactions observed.

Discussion

In this large, binational registry cohort of Australian and New Zealand kidney transplant recipients followed for >90,000 person-years, the incidence of infection-related mortality declined over time and occurred after a median period of 4.1 years after kidney transplantation. Bacterial infections, most commonly pneumonia followed by septicemia and central nervous system infections, accounted for most infectious deaths. Kidney transplant recipients were more likely to die from infection than the age- and sex-matched Australian population with a greater than eight-fold overall higher risk. In the modern era of immunosuppression, infection-related mortality was associated with older age, female sex, Australian Indigenous ethnicity, earlier transplant era, use of T cell–depleting therapy, and deceased donor kidney transplantation.

These findings are in line with those of a Finnish study, which showed that infectious mortality halved between 1990–1999 and 2000–2012 (7). This improvement in infectious death over time was observed despite transplanting older recipients with higher degrees of comorbidity, longer pretransplant dialysis durations, more potent immunosuppressive regimens, and greater utilization of extended criteria donor organs. Potential explanations for the falling rates of infectious death posttransplantation in the present study included changes in immunosuppressive therapies (*e.g.*, introduction of tacrolimus-based immunosuppression from 2005 onward), improvements in infection control measures (*e.g.*, patient charting and increased attention to hand hygiene), more widespread use of antimicrobial prophylaxis (such as cytomegalovirus prophylaxis, perioperative antibiotic administration at the time of transplantation, and long-term *Pneumocystis* prophylaxis), and recommendations to

Table 3. Age-standardized incidence ratio of infectious-related mortality			
Characteristics	General Population Observed Events, *n* (Person-Years at Risk)	Transplant Population Observed Events, *n* (Person-Years at Risk)	SIR (95% CI)
Total population	37,777 (395,306,413)	416 (90,919)	7.8 (7.1 to 8.6)
Men	19,784 (196,444,645)	232 (56,423)	6.2 (5.5 to 7.1)
Women	17,993 (198,861,768)	184 (34,496)	11.4 (9.8 to 13.1)
SIR, standardized incidence ratio; 95% CI, 95% confidence interval.			

Table 4. Factors associated with infection-related mortality among first graft kidney transplant recipients enrolled in Australia and New Zealand

Demographics	No. of Events	Univariable Analysis		Multivariable Analysis	
		SHR (95% CI)	P Value	SHR (95% CI)	P Value
Recipient characteristics					
Age (yr)			<0.001		<0.001
<20	2	0.64 (0.15 to 2.70)		0.55 (0.68 to 4.4)	
20–29	26	1		1	
30–39	59	1.61 (1.01 to 2.56)		1.34 (0.70 to 2.56)	
40–49	107	2.23 (1.45 to 3.42)		1.57 (0.83 to 2.94)	
50–59	131	2.89 (1.90 to 4.42)		2.10 (1.12 to 3.95)	
≥60	91	4.37 (2.81 to 6.77		4.16 (2.15 to 8.05)	
Sex			<0.001		0.002
Men	232	1		1	
Women	184	1.29 (1.07 to 1.56)		1.62 (1.19 to 2.29)	
Ethnicity			<0.001		<0.001
White	297	1		1	
Indigenous	66	3.47 (2.65 to 4.54)		2.87 (1.84 to 4.46)	
Asian	39	1.33 (0.95 to 1.85)		1.21 (0.73 to 2.01)	
Other	14	1.01 (0.59 to 1.72)		1.03 (0.47 to 2.27)	
Country			0.17		0.40
Australia	343	1		1	
New Zealand	73	1.19 (0.93 to 1.53)		1.24 (0.75 to 2.05)	
Body mass index (kg/m^2)			0.89		0.73
<18.5	13	0.88 (0.50 to 1.56)		1.35 (0.67 to 2.72)	
18.5–24	183	1		1	
25–29	136	1.02 (0.82 to 1.27)		0.89 (0.63 to 1.26)	
30–34	60	1.19 (0.89 to 1.60)		0.98 (0.64 to 1.50)	
35–39	15	1.07 (0.63 to 1.81)		0.66 (0.30 to 1.46)	
≥40	9	1.13 (0.46 to 2.73)		0.90 (0.28 to 2.94)	
Primary cause of kidney failure			<0.001		0.04
Glomerulonephritis	159	1		1	
Cystic kidney disease	45	0.94 (0.68 to 1.31)		0.52 (0.28 to 0.99)	
Reflux nephropathy	24	0.78 (0.51 to 1.19)		0.93 (0.46 to 1.92)	
Renovascular	24	1.52 (0.99 to 2.33)		1.64 (0.94 to 2.87)	
Diabetic kidney disease	90	1.95 (1.51 to 2.53)		0.86 (0.44 to 1.68)	
Other	74	1.70 (1.29 to 2.23)		1.39 (0.90 to 2.17)	
Comorbidities (suspected or unknown)			<0.001		0.04
Chronic lung disease	48	2.17 (1.60 to 2.93)		1.71 (1.10 to 2.65)	
Coronary artery disease	115	2.39 (1.93 to 2.96)		1.34 (0.88 to 2.02)	
Peripheral vascular disease	71	2.37 (1.84 to 3.06)		1.69 (1.01 to 2.82)	
Cerebrovascular disease	29	1.62 (1.11 to 2.36)		1.04 (0.59 to 1.85)	
Diabetes mellitus	121	1.97 (1.59 to 2.43)		1.15 (0.72 to 1.84)	
Donor characteristics					
Donor age (yr)			<0.001		0.24
<20	48	1		1	
20–29	39	0.70 (0.46 to 1.08)		0.62 (0.32 to 1.21)	
30–39	48	0.68 (0.46 to 1.02)		0.57 (0.29 to 1.10)	
40–49	80	0.68 (0.47 to 0.97)		0.58 (0.29 to 1.15)	
50–59	101	0.80 (0.57 to 1.13)		0.67 (0.33 to 1.35)	
60–69	71	1.02 (0.71 to 1.48)		0.69 (0.33 to 1.45)	
≥70	29	1.84 (1.16 to 2.93)		1.33 (0.51 to 3.45)	
Donor source			<0.001		0.003
Deceased donor	334	1		1	
Live donor	82	0.42 (0.33 to 0.53)		0.53 (0.37 to 0.76)	
Transplant characteristics					
Era			0.007		0.006
1997–2000	142	1		1	
2001–2005	147	0.88 (0.70 to 1.11)		0.87 (0.55 to 1.37)	
2006–2010	84	0.64 (0.49 to 0.85)		0.61 (0.35 to 1.06)	
2011–2015	43	0.54 (0.37 to 0.77)		0.39 (0.20 to 0.76)	
Baseline immunosuppression			0.12		0.49
Tacrolimus/mycophenolate/prednisolone	127	1		1	
Cyclosporin/mycophenolate/prednisolone	182	0.88 (0.73 to 1.10)		0.85 (0.60 to 1.22)	
Other	107	0.74 (0.66 to 1.01)		0.86 (0.54 to 1.38)	
Antirejection immunosuppression			<0.001		<0.001
No T cell–depleting therapy	343	1		1	
T cell–depleting therapy	73	2.75 (1.99 to 3.81)		2.43 (1.36 to 4.33)	

SHR, subdistribution hazard ratio; 95% CI, 95% confidence interval.

reduce overall immunosuppression in elderly transplant recipients (14–18).

The finding from this investigation that bacterial infection, typically involving the respiratory system, was the most frequent cause of infectious-related mortality also mirrored that of the Finnish study (7). In contrast, a single-center Spanish study of 218 kidney transplant patients between 1995 and 2004 reported that septicemia was the commonest cause of infectious death (35%), followed by pneumonia (18%) (10). The apparent disparity in findings may be explained by regional variations in infection rates and severity, or by variations in coding practices among different registries.

Compared with the age- and sex-matched general population, kidney transplant recipients exhibited an eight-fold greater incidence of infectious death, which was somewhat lower than the 32-fold excess risk reported by a United Kingdom Renal Registry study (8). This difference may relate to regional variations in infection rates and severity, or to different clinical practices with respect to immunosuppression and infection management.

An important finding of this study was the observed sex disparity in risk of infectious death. Compared with men, women experienced a 62% higher risk of infectious death. Moreover, compared with the general population, the SIR of infectious death was considerably higher in women (11.4; 95% CI, 9.8 to 13.1) than in men (6.2; 95% CI, 5.5 to 7.1). The association between female sex and infection-related mortality after kidney transplantation may be due to sex-specific differences in immune responses, sex-specific pharmacokinetic and pharmacodynamic immunosuppressive responses (19,20), and greater degrees of HLA sensitization in women, leading to different immunosuppression approaches (21,22) selection bias and sex-specific differences in the propensity for infection (*e.g.*, greater incidence of urinary tract infections in women) (19,20).

Indigenous ethnicity was also found to be strongly associated with infection-related mortality. This may be related to socioeconomic disadvantage, remoteness of residence, overcrowded living circumstances, and poor access to health care services. There may also be ethnic differences in relation to immune system responses to infection (23). The high infectious burden has led to recent calls for evaluation of modified immunosuppressive regimens in Aboriginal and Torres Strait Islander peoples (23,24).

Another intriguing finding was that deceased donor kidney transplants were associated with higher infection-related mortality. This is consistent with the observations of a meta-analysis of four observational cohort studies involving 1721 participants in which deceased donor kidney transplant recipients had a higher odds of experiencing an infectious complication than living donor kidney transplant recipients (odds ratio, 2.65; 95% CI, 2.05 to 3.41; $P<0.001$) (25). Although the meta-analysis was limited by high heterogeneity (I^2 93%; $P<0.001$) and mostly small studies with suboptimal methodological quality, it is possible that differences in ischemic times, rates of delayed graft function, and possibly immunosuppressant dosages may lead to modification of infectious risk.

The strengths of this study include its very large sample size, inclusion of all Australian and New Zealand patients who received a kidney transplant during a 19-year study period, and the use of robust statistical analyses (including competing risk regression). These greatly enhanced the study's internal validity. These strengths should be balanced against the study's limitations, which included limited depth of data collection. ANZDATA does not collect important information, such as individual unit management protocols, laboratory values, and severity of comorbidities. It is also important to note that there may have been important variations between different transplant units with respect to patient selection and infection prevention strategies, which could have affected the results. Although adjustment was made for many patient characteristics, the possibility of residual confounding could not be excluded. In common with other registries, ANZDATA is a voluntary registry and there is no external audit of data accuracy. Consequently, the possibilities of ascertainment bias, inaccurate coding and misclassification bias cannot be excluded. The ANZDATA registry allowed only one cause of death to be reported, and it is possible that some patients may have had several factors leading to death. Additionally, this study focused only on infectious causes of death, and no data were available about nonfatal infections, which also cause substantial morbidity in kidney transplant recipients. The ANZDATA registry does not provide any information on the immunosuppressive load post-transplant or the emergence of post-transplant diabetes, or crossvalidation of the cause of death with the national death registries of Australia or New Zealand. Moreover, there was no age- and sex-standardized information on the New Zealand population, and as such, specific New Zealand transplant recipients could not be evaluated alone. The study findings may not be generalizable outside of Australia and New Zealand. A further limitation is that this study did not look at center effects.

In conclusion, infection-related mortality among kidney transplant recipients is an important issue. Although infection-related mortality has decreased over time, approximately one fifth of kidney transplant recipients died from infection after a kidney transplant and the majority of these patients died with a functioning graft. Higher infection-related mortality was associated with older age, female sex, Indigenous ethnicity, earlier transplant era, use of antithymocyte globulin, and deceased donor kidney transplantation. This information may help better inform shared decision making by patients and clinicians.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.03200319/-/DCSupplemental.

Supplemental Table 1. Total missing numbers for each baseline characteristic.

Supplemental Table 2. A map of the causes of death to the categories of death in this ANZDATA cohort study.

Supplemental Table 3. Specific pathogens associated with infection-related mortality.

Supplemental Figure 1. (A) Overall organism-specific incidence mortality rates, following 12 months of transplantation, by transplant era. (B) Overall site-specific incidence mortality rates, after 12 months of transplantation, by transplant era. Error bars depict the upper 95% confidence limit.

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