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Acute Rejection, Overall Graft Loss, and Infection-related Deaths After Kidney Transplantation in Indigenous Australians

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Introduction: Aboriginal and Torres Strait Islander peoples (hereafter respectfully termed Indigenous Australians) experience a 3-fold increased risk of acute rejection after transplantation compared to non-Indigenous Australians. We investigated whether acute rejection explains the association between Indigenous status, infection-related deaths, and all-cause deaths after kidney transplantation, and whether acute rejection mediates the relationship between Indigenous status and overall graft loss.

Methods: This cohort study included all recipients who received their first kidney transplant between 2005 and 2018 in Australia, using data from the Australia and New Zealand Dialysis and Transplant registry. Multivariable Cox regression models determined the associations between Indigenous status, graft loss, infection-related deaths, and all-cause deaths. Mediation analyses examined if acute rejection mediated these relationships. Primary outcome was infection-related death. Secondary outcomes included all-cause death and overall graft loss.

Results: There were 9993 patients ($n = 390$ (3.9%) Indigenous Australians) who received a kidney transplant between 2005 and 2018, and they were followed-up with for 56,876 patient-years. A total of 1165 died (12%) (211 infection-related deaths) and 1957 (20%) lost their allografts. Compared with non-Indigenous recipients, the adjusted hazard ratio (HR) (95% confidence interval [CI]) for graft loss, infection-related deaths and all-cause deaths among Indigenous Australians were 2.27 (1.90–2.71), 3.01 (1.90–4.77) and 2.36 (1.89–2.94), respectively. The mediation analysis showed the association between Indigenous status and graft loss (but not infection-related death or all-cause death) was partially mediated by acute rejection (1.06 [1.03–1.09]), and the proportion of effects mediated by acute rejection was 0.10.

Conclusion: Indigenous Australians experienced a higher risk of graft loss, a relationship mediated partially through acute rejection. The higher risk of infection-related death was independent of acute rejection.

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KEYWORDS: acute rejection; health equity; indigenous; mediation analyses; transplantation

Indigenous Australians are disproportionately affected by kidney failure, with an incidence almost 7 times greater than non-Indigenous people in Australia.[1] Kidney transplantation is the preferred treatment modality for most patients with kidney failure because it confers a survival advantage and improves quality of life compared to maintenance dialysis.[2,3] Yet, Indigenous Australians are less likely to be included in the deceased donor transplant waiting list and less likely to receive a kidney transplant after listing,[4] a disparity which cannot be adequately explained by patient-related or disease-related factors, such as age, sex, comorbidities, or cause of kidney disease.[4,5] Even with transplantation, disparate outcomes are observed, with the overall risk of graft loss and mortality at least 4 times higher among Indigenous Australians, compared to non-Indigenous Australians.[6]

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The contributing risk factors are likely to be multifactorial and may include social determinants of health, access to culturally appropriate care, institutional racism and differences in vascular risk burden, and immunological compatibility between donor and recipients.[4,7-11]

The current Australian deceased donor allocation algorithm prioritizes recipients who are highly sensitized with maximum panel reactive antibody between 95% and 99%. This is followed by optimal human leukocyte antigen (HLA)-A, B, and DR matching in recipients with lower expected post-transplant survival scores. Indigenous Australians living with kidney transplants have dissimilar HLA types compared to non-Indigenous Australians,[12-14] and therefore are less likely to receive HLA-compatible donor kidneys sourced predominantly from European Australians. Without a favorable HLA profile, Indigenous Australians spend longer time on dialysis before receiving a transplant.[15] The unfavorable HLA matching may also predispose Indigenous Australians to a 3-fold greater risk of severe rejection such as vascular and antibody mediated rejection compared to non-Indigenous Australians.[6] Treatment of these severe rejection episodes often requires intensive additional immunosuppressiives such as T and B cell depleting agents. There is evidence suggesting that these interventions may increase the risk of fatal opportunistic infections, and consequently premature death.[6,16-19] Various studies have shown that the risk of infection-related death among Indigenous Australians doubles that of non-Indigenous Australians in the general population.[20,21]

The primary objective of this study was to investigate whether acute rejection explained some of the association between Indigenous status, infection-related deaths, and all-cause deaths. We also confirmed the association between Indigenous status and overall graft loss and determined whether acute rejection mediated the relationship between Indigenous status and overall graft loss in a national cohort of kidney transplant recipients.

METHODS

Indigenous Community Involvement and Ethics

This project was cocreated by nephrologists with extensive knowledge in working with Indigenous transplant patients, with aims emerging from stakeholder priorities. We sought input from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Aboriginal and Torres Strait Islander Health Working Group, and 1 coauthor, JTH was the Chair. Two coauthors are themselves Indigenous, namely JTH who is Torres Strait Islander and VS who is Aboriginal. The project findings will be disseminated to local communities, including Aboriginal Medical Services, Aboriginal health care workers, and the ANZDATA Aboriginal and Torres Strait Islander Health Working Group, in a holistic and culturally appropriate manner. This study was approved by the University of Western Australia Human Research Ethics Committee (dated May 11, 2018, Ref: RA/4/20/4539). The design, conduct and reporting are in accordance with the Strengthening the Reporting of Observational studies in Epidemiology.[22]

Study Population

Using data from the ANZDATA registry, we included all kidney transplant recipients who received their first kidney transplants between 2005 and 2018 in Australia. The ANZDATA collects data on consenting (>99%) patients receiving kidney replacement therapy in Australia and New Zealand. Its methods are described at its website (http://www.anzdata.org.au). Recipients who had received multiple organ allografts, prior allografts, and kidney transplant recipients from New Zealand were excluded (Figure 1).

Data Collection

We included baseline donor characteristics such as donor age, sex, ethnicity, and source (living or deceased); recipient characteristics such as age, sex, ethnicity, comorbidities at time of transplant, primary cause of kidney failure; and transplant-specific characteristics such as HLA mismatches, panel reactive antibody, total ischemic time, induction therapy, initial immunosuppressive agents, and transplant era.

Recipient ethnicity is coded in the ANZDATA registry as a self-reported variable. We have recoded ethnicity into Indigenous Australian (if the recipient identifies as Aboriginal and/or Torres Strait Islander) and into non-Indigenous Australians for all other recipients. In this analysis, we included all acute rejection episodes. Episodes of rejection (both late and early) of the date of surgery have been collected by the registry since 2004. For each episode, the treating physician is asked to report whether the episode was proven by a biopsy. Biopsies were processed locally and interpreted by the local histopathologist. For biopsy-proven episodes of rejection, the presence of cellular, glomerular, and vascular rejection, as well as the acute Banff indices were reported. If biopsies were not performed, then the diagnosis of acute rejection was defined based on clinical grounds (including response to treatment). Because detailed treatment data was not consistently reported, they were not included in this study.[23] The actual data reporting form can be observed at the website of ANZDATA (https://www.anzdata.org.au/wp-content/uploads/2016/10/5AcuteRejectionForm2017.pdf).

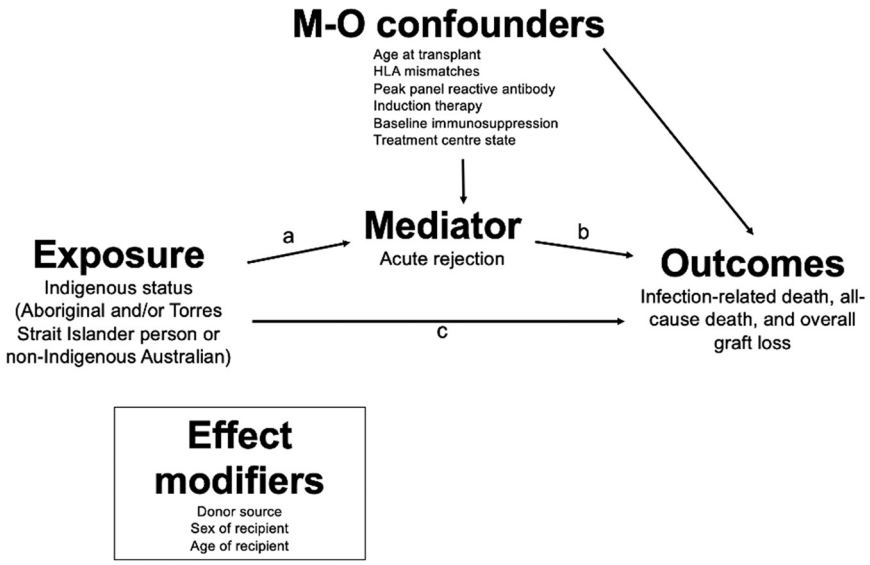

Figure 1. Directed acyclic graphs of the potential causal relationships between ethnicity and outcomes of interest (infection-related death, all-cause death and overall graft loss). (M-O confounders, mediator-outcomes confounders).

Outcomes

The primary outcome of this study was infection-related death. The diagnoses of cause-specific death were coded in the ANZDATA registry and cause of death was assigned to infection (A00–B99) according to the International Classification of Disease-10 for mortality classification. Secondary outcomes included all-cause death and overall graft loss (including allograft loss and all-cause death).

Statistical Analysis

Baseline characteristics were expressed as number (proportion), mean and SD, and median and interquartile range, where appropriate. Comparison of baseline characteristics by exposure groups (Indigenous and non-Indigenous Australians) were undertaken using chi-squared test, Analysis of Variance and Mann-Whitney *U* test, respectively. Missing values (for all covariates) were imputed using multiple chained equation using fully conditional specification with the *mice* package (version 3.6.0) for R (version 3.6.1, The R Foundation for Statistical Computing, Vienna, Austria). A total of 421 data sets were imputed, and variables with missing data were donor age (0.3% missing), donor sex (0.3%), ethnicity of donor (1.16%), ethnicity of recipient (2.0%), primary cause of kidney failure (1.5%), comorbidities at transplant (1.5%) and HLA (1.5%). For donor age, we used predictive mean matching for the imputation due to its skewed distribution in this population. For other categorical variables, imputation was done by logistic regression (binary outcome) or ordinal logistic regression (ordinal categorical with >2 levels). Significance levels were set at *P* value of 0.05 and hypothesis tests were 2-sided. We used the survival package[24] in R version 4.0.3 (The R Foundation for Statistical Computing) for all analyses except for the mediation analysis for which we used the macro by Valeri and VanderWeele in SAS 9.4 (SAS Institute, Cary, NC).[25]

Survival Analyses

For the survival analyses, the follow-up times were defined from the time of transplantation until the time when the outcome of interest occurred. For infection-related death, censoring occurred at other causes of death, end of the follow-up period (December 31, 2018) or loss to follow up. For overall graft loss (inclusive of graft loss and all-cause death), censoring occurred at the end of the follow-up period or at loss to follow up. The proportion of transplant recipients free of the events of interest was calculated using Kaplan-Meier method.

Cox proportional hazard models were conducted to assess the relationship between the exposure (Indigenous status) and the prespecified outcomes, including infection-related death, all-cause death and overall graft loss. All variables that had an association between infection related death, all-cause death and overall graft loss (that is, a change in the beta-coefficient by 10% or more) were included in the multivariable analyses (Supplementary Table S1). Five potential effect modifiers between the exposure and other covariates was assessed using 2-way interaction terms, which were HLA mismatches, donor diabetes at time of transplant, donor source (living vs. deceased), sex, and age of recipient. However, no interactions were found. The proportional hazards assumptions of all Cox models

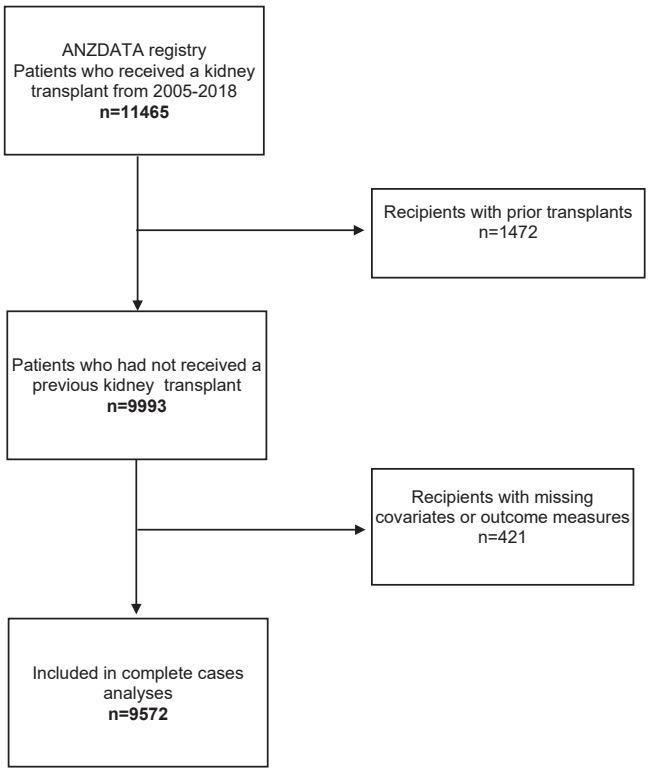

Figure 2. Flowchart of study participants in complete cases analyses.

were assessed by fitting log(time) dependent covariates in the multivariable model and checked graphically by plotting the Schoenfeld residuals. No variables deviated from the proportional hazards assumption.

Mediation Analyses

A directed acyclic graph for the study showing the potential causal relationship between Indigenous status and outcomes is shown in Figure 2. We assessed (a) the association between Indigenous status and acute rejection, (b) the association between acute rejection and outcomes using Cox regression models. We then assessed the controlled direct effects (c) of Indigenous status on the outcomes using a Cox-regression model. Details of the mediation and sensitivity analyses are included in supplementary methods.

RESULTS

Study Population

A total of 11,465 patients with kidney failure received a kidney transplant (3398 deceased and 6595 living) during the study period. Of these, 9993 patients received their first kidney transplants, including 390 (3.8%) Indigenous Australians. Table 1 shows the baseline characteristics stratified by Indigenous status. Indigenous Australians were more likely to have coexisting comorbidities at time of transplant,

Table 1. Recipient characteristics of kidney transplant recipients stratified by ethnicity between 2005 to 2018 ($N = 9993$)

Characteristic	Nonindigenous Australians n (%) ($n = 9603$)	Indigenous Australians n (%) ($n = 390$)	*P*-values
Female	3457 (36.0)	175 (44.9)	0.046[e]
Age at transplant			<0.001[e]
<30 yr	1254	54	
31–50 yr	3275	187	
>50 yr	5074 (52.8)	149 (38.2)	
Ethnicity			<0.001[e]
Aboriginal	0 (0.0)	373 (95.6)	
Torres Strait Islander	0 (0.0)	17 (4.4)	
Nonindigenous Australian	9603 (100.0)	0 (0.0)	
Index of Relative Socio-economic Disadvantage			<0.001[e]
1	953 (9.9)	81 (20.8)	
2–9	7223 (75.2)	282 (72.3)	
10	922 (9.6)	5 (1.3)	
Not reported	505 (5.3)	22 (5.6)	
Diabetes	1724 (18.0)	182 (46.7)	<0.001[e]
Peripheral vascular disease	847 (8.8)	60 (15.4)	<0.001[e]
Coronary artery disease	1675 (17.4)	115 (29.5)	<0.001[e]
Cerebrovascular disease	529 (5.5)	33 (8.5)	0.023[e]
Lung disease	717 (7.5)	53 (13.6)	<0.001[e]
Cause of kidney failure			<0.001[e]
Glomerulonephritides	3898 (40.6)	136 (34.9)	
Diabetes	1129 (11.8)	145 (37.2)	
Cystic diseases	1550 (16.1)	8 (2.1)	
Other	3031 (31.6)	101 (25.9)	
Donor age			0.053
<30 yr	1299 (13.5)	65 (16.7)	
31–50 yr	3560 (37.1)	153 (39.2)	
>50 yr	4744 (49.4)	172 (44.1)	
Donor type			<0.001[e]
Live	3360 (35.0)	38 (9.7)	
Deceased	6243 (65.0)	352 (90.3)	
Donor ethnicity			<0.001[e]
Caucasian	8563 (89.2)	349 (89.5)	
Indigenous Australian	181 (1.9)	18 (4.6)	
Other	769 (8.0)	19(4.9)	
HLA-ABDR mismatches[a]			<0.001[e]
0	4174.3)	3 (0.8)	
1–2	2575 (26.8)	57 (14.6)	
3–4	3264 (34.0)	101 (25.9)	
5–6	3347 (34.9)	229 (58.7)	
Peak PRA[b]			<0.001[e]
0–10%	8200 (85.4)	312 (80.0)	
11–50%	949 (9.9)	48 (12.3)	
>50%	454 (4.7)	30 (7.7)	
Induction			0.16
None	1000 (10.4)	44 (11.3)	
IL-2 receptor antibody	8212 (85.5)	321 (82.3)	
T-cell depleting agents	391 (4.1)	25 (6.4)	
Regimen			<0.001[e]
Prednisone, MMF[c], Tacrolimus	7797 (81.2)	354 (90.8)	
Prednisone, MMF, Cyclosporin A	120 (1.2)	24 (6.2)	
	53 (0.6)	1 (0.3)	

(Continued on following page)

Table 1. (Continued) Recipient characteristics of kidney transplant recipients stratified by ethnicity between 2005 to 2018 ($N = 9993$)

Characteristic	Nonindigenous Australians n (%) ($n = 9603$)	Indigenous Australians n (%) ($n = 390$)	*P*-values
Prednisone, Azathioprine, CNI[d]			
Other	523 (5.5)	11 (2.8)	
Acute rejection	2457 (25.6)	136 (34.9)	<0.001[e]

CNI, calcineurin inhibitor; HLA, human leukocyte antigen; IL, interleukin; MMF, mycophenolate mofetil; PRA, panel reactive antibody.
[a]Human leukocyte antigen A, B, DR mismatches.
[b]Panel reactive antibody.
[c]Mycophenolate mofetil.
[d]Calcineurin inhibitor, e.g., Cyclosporin A, Tacrolimus.
[e]$P < 0.05$.

including diabetes mellitus (47.0% vs. 18.0%), peripheral vascular disease (15.6% vs. 8.7%), lung disease (13.3% vs. 7.5%), cerebrovascular disease (8.4% vs. 5.5%) and coronary artery disease (30.0% vs. 7.4%). A greater proportion were also highly sensitized (panel reactive antibody >50%; 7.8% vs. 4.7%) and they were more likely to receive 5 to 6 HLA-mismatched kidneys (58.2% vs. 35.0%), compared to their non-Indigenous counterparts. Similarly, the proportion of Indigenous Australians who experienced acute rejection was greater (34.7% vs. 25.6%) than non-Indigenous Australians.

Causes of Infection-related Death

Within the study population, 211 patients (2.1%) died of infection-related causes. The leading causes of infections related deaths were bacterial (87/211, 41.2%) followed by fungal infections (53/211, 25.1%) (Supplementary Table S2). Lung and septicemia were the 2 most common sources of infection (81/211, 38.4% and 72/211, 34.1%, respectively) (Supplementary Table S3).

Association Between Indigenous Status, Infection-related Death, All-cause Death and Overall Graft Loss

The Kaplan-Meier survival curves for these 3 outcomes are shown in Figure 3. The 1-year and 5-year patient survival (%) (95% CI) were 95.7 (93.6, 97.8) and 82.8 (78.8, 87.4) for Indigenous Australians and 98.1 (97.8, 98.4) and 92.2 (91.5, 92.8) for non-Indigenous Australians. The 1-year and 5-year graft survival (%) (95% CI) were 92.5 (89.9, 95.3) and 69.5 (64.2,75.1) for Indigenous Australians and 95.4 (95.0, 95.8) and 85.4(84.6,96.2) for non-Indigenous Australians. In the multivariable-adjusted analyses, compared to non-Indigenous Australians, Indigenous Australians experienced a higher risk of infection-related death (HR [95% CI]): 3.01 (1.90–4.77), all-cause death: 2.36 (1.89–2.94), and overall graft loss: 2.27 (1.90–2.71).

Mediation Analyses

Association Between Ethnicity and Acute Rejection

The median time to first acute rejection was 59 days (interquartile range = 286 days), with 44.5% of episodes of acute rejections occurring within the first month post-transplant. Compared to non-Indigenous Australians, the HR for acute rejection among Indigenous Australians (95% CI) was 1.48 (1.24–1.77).

Association Between Acute Rejection and Infection-related Death, All-cause Death, and Overall Graft Loss

Recipients who developed acute rejection were more likely to experience infection-related death and all-cause death compared to recipients who did not experience acute rejection, adjusted for age, HLA mismatches, baseline immunosuppression, induction and panel reactive antibody [adjusted HRs (95% CI) of 1.36 (0.84–1.53) and 1.21 (1.06–1.37) respectively]. Those who developed acute rejection were also more likely to have overall graft loss (HR of 1.72 [95% CI 1.57–1.88]).

Estimates of the Direct (C), Indirect (A+B) and Total Effects

The estimates of the direct, indirect and total effects of Indigenous status on infection-related death, all-cause death and overall graft loss are shown in Table 2. Indigenous Australians experienced a higher risk of all-cause death and infection-related death, but this association was not mediated through acute rejection (HR [95% CI] of 1.01 [0.98–1.04] and 1.00 [0.99–1.01]). The association between Indigenous status and overall graft loss was mediated by acute rejection: HR (95% CI) 1.06 (1.03–1.09). The proportion of the effect of Indigenous status on overall graft loss that was mediated by acute rejection was 0.096 (i.e., 9.6% of the effect of Indigenous status on graft loss was explained by acute rejection).

Diabetes as a Mediator in the Association Between Indigenous Status and Outcomes

Diabetes status at the time of transplantation was also a mediator between Indigenous status and graft loss HR (95% CI) (1.23 [1.16–1.29]), infection-related death (1.28 [1.13–1.46]) and all-cause death (1.31 [1.22–1.39]). Specifically, the proportions of the effect of Indigenous status, mediated by recipient diabetes status at time of transplant, on infection-related death, all-cause death, and overall graft loss were 0.29, 0.34 and 0.31, respectively.

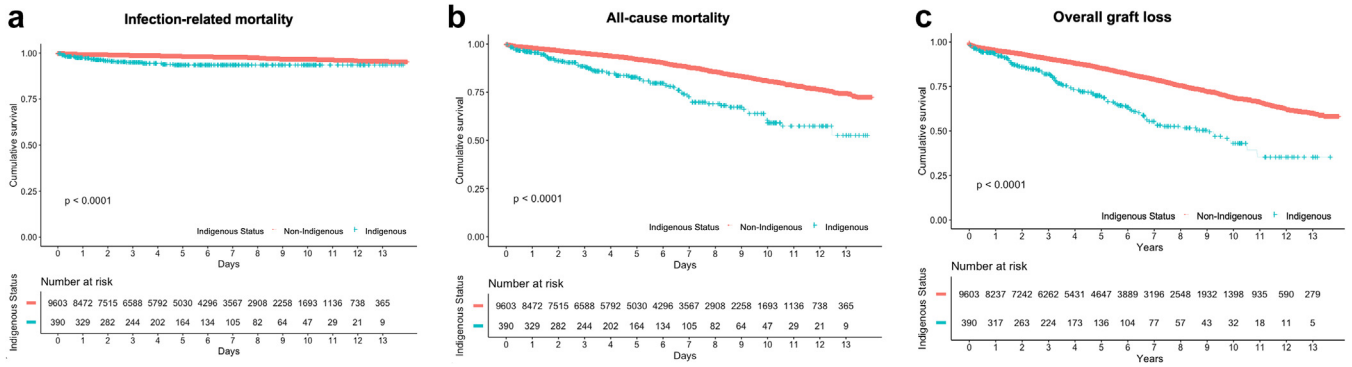

Figure 3. Kaplan-Meier estimates of infection-related death (a), all-cause death (b) and overall graft loss (c), stratified by ethnicity

Sensitivity Analyses

The complete case analyses findings were similar to that of the imputed data. Compared to non-Indigenous Australians, the HR (95% CI) for infection-related death, all-cause death, and overall graft loss among Indigenous Australians were 3.01 (1.90–4.77), 2.32 (1.85–2.91), and 2.28 (1.90–2.73), respectively, and the E-values were 2.06, 1.71 and 2.33 respectively. In the competing risk analysis for infection-related death, with non-infection related deaths as competing events, the adjusted subdistributional HR (95% CI) for infection-related death in Indigenous Australians was 2.81 (1.77–4.48) compared to non-Indigenous Australians (Figure 4).

DISCUSSION

In this very large cohort of kidney transplant recipients, we found an approximately 3 times increased risk of infection-related death among Indigenous Australians compared with non-Indigenous Australians. Similarly, the risks of allograft loss and all-cause death were doubled compared to non-Indigenous Australians. In our mediation analyses, we found that acute rejection lies in the causal pathway in the association between Indigenous status and allograft loss, but the relationship between Indigenous status, infection-related and all-cause death was not mediated through acute rejection. We also found that recipient diabetes status at the time of transplantation was a mediator between Indigenous status and the outcomes, including graft loss, infection-related and all-cause death.

Our current findings corroborate those previously reported in a smaller single-center study of 616 kidney transplant recipients in Western Australia, of which 57 (9%) were Indigenous recipients.[18] In this study, the authors found the rate of biopsy-proven acute rejection was almost doubled in Indigenous recipients, with an excess of antibody-mediated rejections. Acute rejection was found to mediate the effect between ethnicity and death censored graft loss, but not death with a functioning graft. However, this study did not specifically evaluate cause-specific mortality. Our current results built upon these previous findings and showed that the risk of biopsy-proven acute rejection was least twice as high among Indigenous Australians compared to the non-Indigenous population, and that acute rejection was a potential mediator between Indigenous status and overall graft loss. However, the magnitude of the effects mediated by acute rejection was smaller compared to previous analyses. In this current study, acute rejection accounted for 10% of the association between ethnicity and overall graft loss. This differed from the Western Australian cohort where the effects mediated through rejection was at least 70%. There may be multiple reasons for the observed differences. In this analysis, we assessed overall graft loss, whereas in the Western Australian cohort, only death-censored graft loss was evaluated. Also, a single mediator was considered. There may be other multiple path-specific

Table 2. Estimates of the direct and indirect effects of ethnicity on infection-related death, all-cause death and overall graft loss

Effects	Infection-related death			All-cause death			Overall graft loss		
	Estimates	95% CI	*P*-values	Estimates	95% CI	*P*-values	Estimates	95% CI	*P*-values
Natural direct effects	2.97	1.87 – 4.72	<0.001[a]	2.37	1.90 – 2.96	<0.001[a]	2.15	1.80 – 2.57	<0.001[a]
Natural indirect effects	1.01	0.98 – 1.04	0.52	1.00	0.99 – 1.01	0.53	1.06	1.03 – 1.09	<0.001[a]
Total effects	3.00	1.89 – 4.76	<0.001[a]	2.36	1.89 – 2.95	<0.001[a]	2.28	1.90 – 2.73	<0.001[a]
Proportion of effect of ethnicity mediated by acute rejection		0.01			−0.01			0.10	

CI, confidence interval.
[a]$P < 0.05$.

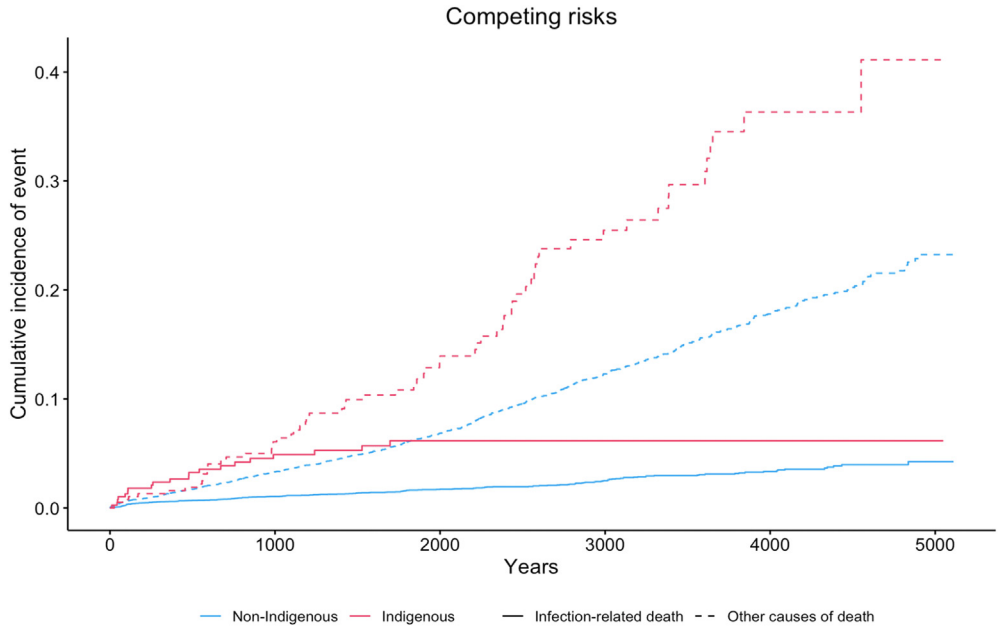

Figure 4. Comparison of cumulative incidence function of infection-related mortality with competing-risk of other causes of mortality stratified by ethnicity. ANZDATA, Australia and New Zealand Dialysis and Transplant Registry

effects through 2 or more mediators, such as tacrolimus drug levels, causally ordered between ethnicity, acute rejection, and graft loss. We could not investigate all the potential mediators because details regarding the intensity of baseline immunosuppression, drug levels, and medication adherence were not collected by the registry.[26] There may also be potential pharmacokinetic differences in drug exposure between Indigenous and non-Indigenous Australians. Moreover, there may be other potential mediators between ethnicity and graft loss, which may not causally affect each other. For example, comorbidities, including diabetes, vascular disease, and other recipient or donor immune compatibility may independently affect graft loss, but detailed assessment of each of these individual factors are outside the scope of this study. In addition, a single version of the mediator as a binary variable of acute rejection was defined. Nevertheless, there are many versions of acute rejection, including biopsy-proven borderline, subclinical, cellular, antibody, and mixed rejection. It is likely that what was estimated as a direct effect may in fact have selected not only the direct effect between ethnicity and graft loss, but also the mediated effect through other versions of the mediator.[27] Therefore, in this context, this may have led to the overestimation of the direct effect and an underestimate of the indirect effects. However, the framework from this study will provide future opportunities to examine whether acute rejection may mediate other causes of graft loss or death associated with ethnicity.

In this study, we hypothesized that the increased risk of infection-related death in Indigenous transplant recipients may be in part due to the increased baseline immunosuppression load after episodes of acute rejection.[28] However, our current findings refute the notion that acute rejection *per se* was a key factor responsible for the observed disparate mortality outcomes between Indigenous and non-Indigenous Australian kidney transplant recipients. Other reasons, such as inequitable health system experiences, the lack of accountability for translating health care policies into practice, experiences of racism, and other socio-political and environmental factors may be root-causes of the higher risk of all-cause and infection-related death in Indigenous populations.[29] Most interventions have focused on mitigating proximal risk factors, but many have failed to address the underlying distal social and structural determinants that underpin poor health in disadvantaged populations. This is seen even in access to transplantation, where socioeconomically disadvantaged groups are less likely to receive living donor kidneys.[30,31] As illustrated in our baseline characteristics table, Indigenous Australians are less likely to receive a kidney from a living donor; the contributing factors include a lack of culturally safe promotion of transplantation and the increased medical comorbidities that render potential donors high risk.[32] To this effect, an unacceptable gap remains in both the quality of life and survival outcomes for Indigenous transplant recipients compared to their non-Indigenous counterparts. To address this gap, a whole of government and transplant community commitment is needed.

Direct engagement with Indigenous health professionals to better understand cultural and social

determinants of health is crucial. Victim blaming on issues such as medication adherence by the health care system and health professionals will only reinforce the predominant view of "health" determined by mainstream Western biomedical theory,[9] without full consideration of culturally appropriate practices to address the health disparity. A key element to improve post-transplant outcomes in Indigenous Australians is provision of personalized, culturally sensitive, non-"one-size-fits all" care management pathways in both remote and urban settings.[33] This can only be achieved through positioning of Indigenous health professionals as leaders, engagement with the communities, as well as direct engagement and collaboration with families and their caregivers.[34]

Minister Ken Wyatt AM MP convened the Renal Health Roundtable in 2018[35] that recommended the design of an inaugural National Renal Health RoadMap. Recognizing the cross-jurisdictional responsibility of both federal, state, and Territory Health Ministers, the RoadMap was also endorsed by the Australian Health Ministers Advisory Council in 2019. We note the National Renal Health RoadMap is currently unfunded, although its implementation is likely to address many of the environmental health and social determinants of health factors contributing to outcomes in this analysis. We stand with the Australian community, in seeking funding and implementation of this multijurisdictionally endorsed policy.

There are several strengths to this study. Notably, the large sample size, completeness of data, with sufficient follow-up time, and the use of robust statistical analyses (including competing risk regression and multiple imputation) all added to the internal validity of this study. There are also potential limitations. The ANZDATA registry does not collect individual-level measures of socioeconomic status or access to health care service delivery. Though we adjusted for multiple confounding factors in the indirect pathways between acute rejection, death and overall graft loss, there may be other residual confounders that were not recorded and therefore could not be accounted for. We did not adjust for other baseline variables with the evaluation between race and death in the direct pathway because none of these variables will confound the effect of race. The only potential variable that could theoretically be adjusted for as a confounder is a "historical process," such as genetic and other parental factors that define our race or ethnicity.[36] We acknowledge there may be many mediators between ethnicity and outcomes, but in this analysis, we have focused on acute rejection and excluded potential mediators to avoid the risks of overadjustment.[37] There are no reliable tools to externally check the accuracy of the data in the ANZDATA registry. Previous studies show that the concordance of death registry data between ANZDATA and the National Death index in primary cause of death is fair.[38] This can be partially explained by the absence of diabetes and kidney failure as causes of death in ANZDATA and the absence of "withdrawal from treatment" in the National Death Index. Though misclassification bias or inaccurate coding cannot be excluded, other audits have found favorable data accuracy in the ANZDATA registry.[39] Lastly, details of infection complications (apart from infection-related death) are not recorded in ANZDATA, therefore further investigation into precursors of infectious events are not available.

Acute rejection appears to lie on the causal pathway between ethnicity and graft loss. Therefore, by modifying the risk of acute rejection we can potentially prevent a proportion of allograft loss among Indigenous Australians. Nevertheless, it appears that this would not affect the disparate outcomes in all-cause death or infection-related death between Indigenous and non-Indigenous Australians, because these were not mediated by acute rejection. The pathways between ethnicity, and graft loss and death are likely complex and multifactorial, with multiple drivers of inequities in survival between Indigenous and non-Indigenous transplant recipients. Future investigations need to investigate these structural drivers of inequity, and accordingly implement culturally appropriate care and interventions focused on addressing these drivers.

DISCLOSURE

All the authors declared no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental Methods

Table S1. Univariable Cox regression analyses for infection-related death.

Table S2. Type of infection in infection-related mortality by ethnicity.

Table S3. Location of infection in infection-related mortality by ethnicity.

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