Identification of factors affecting access to Kidney transplant waiting list and outcomes among Indigenous Australians

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October 2020

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Thesis abstract:

Improving access to the waiting list and kidney transplantation is one of the important factors in improving poor outcomes faced by Aboriginal and Torres Strait Islanders (Indigenous) Australians with end stage kidney disease (ESKD). This thesis was designed to address the following specific aims:

- To identify the time to placement on the transplant waiting list and time to transplantation among Indigenous Australians as compared to non-indigenous Australians

- To examine predictors of placement on the transplant waiting list (and non-listing) for kidney transplantation utilising existing data from Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which holds waiting list data from the National Organ Matching System.

- To examine relationships between Indigenous patients' facility haemodialysis attendance and the chance of placement on the transplant waiting list, transplantation and transplant outcomes.

- To identify risk factors predictive of good vs poor outcome following transplantation among Indigenous recipients, through quantitative studies utilising existing ANZDATA Registry data

Research conducted for this thesis confirmed the increased use of haemodialysis along with low numbers of kidney transplantation among Indigenous Australians as compared to non-indigenous Australians. Lower numbers of kidney transplant among Indigenous Australians were further explored to find whether this related to placement on the transplant waiting list and to define the groups who were affected by this. A reduction in placement on the transplant waiting list among Indigenous

Australians more so among people from remote areas was identified. A significant gap in transplantation among Indigenous Australians existed in and after the second year on the transplant waiting list. For this and other research conducted in this thesis, remoteness was defined by Australian Bureau of Statistics (ABS) remoteness categories, by linking ABS postcode of residence concordance data with the postcode recorded in the ANZDATA record for the start of RRT.

Research conducted to explore the association of facility dialysis attendance in Indigenous Australians with ESKD and placement on the transplant waiting list and transplant outcomes was limited by the low number of outcomes measured. An association between placement on the transplant waiting list and transplant outcomes was not evident; however, the chance of transplantation was low among participants with dialysis attendance ≤2.5 sessions/week.

Identification of risk factors predictive of good vs poor outcome following transplantation among Indigenous recipients was conducted by linkage of hospital-derived data with data from the Registry. A cohort study comparing pre and post-transplant hospitalisation among Indigenous kidney transplant recipients of South Australia and Northern Territory found increased rates of hospital admissions, prolonged hospital stay, and increased rates of infection more so in the first year post-transplant. Half of the study participants in our study cohort had delayed graft function. Total ischaemia time was more than 16 hours in half of the study population. Finally, a retrospective case-control study among Indigenous transplant recipients, to explore specific risks factors in the pre-transplant period, showed increased rates of hospitalisation to be predictive of early graft loss. No correlation was found between other studied factors and graft loss (including patients' death).

More studies, including studies to understand pharmacokinetics and pharmacodynamics of immunosuppression in Indigenous transplant recipients, are required to look for other factors not examined here. Hospitalisation in the pre-transplant period needs further exploration and measures identified to reduce these events and complications which follow. Policies need to focus in the first year post-transplant to reduce the burden of hospitalisation. Individually tailored, evidence-based protocols are required to improve the management of post-transplant infections, which may include consideration of broad anti-infective agents. Finding ways to reduce ischaemia time and delayed graft function as a result of this factor need consideration.

Development of algorithms and outcome predicting tools taking into account pre-transplant hospitalisation into the equation may be helpful. Strategies need to be developed to increase placement on the transplant waiting list and transplant rates.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or tertiary institution. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference has been made. I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide.

I acknowledge that the copyright of published works contained within this thesis resides with the copyright holders of those works.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Namrata Khanal Date: 7/08/2021

Acknowledgements:

I would like to thank my supervisors Stephen McDonald, Alan Cass and Paul Lawton, for helping me through the course of PhD.

This work would not have been possible without the ANZDATA Registry, and constant support and encouragement from the lovely staff in the registry. Over the years, we have grown into family and friends- each of you will remain close to my heart.

A big thank you to Drs- Sajiv Cherian, William Majoni, Asanga Abeyaratne, and Mrs Kerry Dole (transplant nurse co-ordinator) for your help during the data collection; South Australian, Top-End and Central Australian Indigenous representatives and also the facilitators Sarah Brown and Heather Hall. I would like to thank medical records and administrative staff of all the hospitals included in the studies for making the foundation of data collection so much easier and smooth.

Statistical help from Phil Clayton, Hannah Dent, Nancy Briggs, Aarti Gulyani, Shahid Ullah and Chris Davies is highly appreciated. I would like to thank Matthew Jose for his contribution as co-author. Thank you Erandi Hewawasam, Mandy / Brian Farmer, Louise McDonald and Roy Sneddon for proofreading some of the chapters and manuscripts for publications. Thank you, Paul, for opening your house to me. While data collection could have been strenuous and boring, cooking in your new kitchen together with your wife (Megan Lawton) and kids made it easy and exciting to wake up next morning and repeat the process.

Thanks also to my family and friends for helping me stay motivated and believing in me.

I would like to pay my sincere respect to all Indigenous Australians- past present and emerging. This research is dedicated to you.

“Together we will close the Gap”

Three things cannot be long hidden

The sun, the moon and the truth

Buddha

List of publications:

1. Khanal N, Clayton P, McDonald S, Jose M. Overview of dialysis in indigenous compared to non-indigenous Australians. Clinical Nephrology. 2016 Jul 29. DOI: 10.5414/cnp86s119.

2. Khanal N, Lawton PD, Cass A, McDonald SP. Disparity of access to kidney transplantation by Indigenous and non-Indigenous Australians. Med J Aust. 2018 Sep 17;209(6):261-6.

3. Khanal N, Lawton PD, Cass A, McDonald SP. Pre and post-transplant hospitalisation in Aboriginal and Torres Strait Islander kidney transplant recipients in South Australia and Northern Territory. (Submitted)

4. Khanal N, Lawton PD, Cass A, McDonald SP. A retrospective case-control study exploring factors for loss of kidney transplant function or death among Indigenous kidney transplant recipients. (Submitted)

1. Introduction

The most severe form of chronic kidney disease (CKD), also known as end stage kidney disease (ESKD), has a significant impact on the health of an individual and health-related expenditure of the nation. (1) The burden is even more significant for Aboriginal and Torres Strait Islander peoples (hereafter respectfully referred to as Indigenous Australians) in Australia. (2) While Indigenous Australians represent 2.8% of the total Australian population, (3) approximately 10% of all the patients receiving dialysis for treatment of ESKD are identified as of Indigenous origin. (4, 5) Dialysis includes haemodialysis (HD) and peritoneal dialysis (PD) and is one of the treatment modalities used for the treatment of patients with ESKD. Other modalities of treatment are kidney transplantation or supportive care. Together, dialysis and kidney transplantation are referred to as kidney replacement therapy (KRT).

Of all these treatment modalities, kidney transplantation is associated with improved quality of life and is cost-effective when compared to dialysis. This advantage is seen even after transplantation of marginal quality kidneys (6) and irrespective of dialysis vintage. (7) In addition, survival benefits and reduced risk of cardiovascular events have been described in those receiving kidney transplants. (7) Benefits of transplantation are independent of the dialysis modality, deceased, or living donors. (7) It is, therefore, the preferred treatment option for ESKD where medically possible. (8, 9) It is absolutely vital that every effort is made to increase the number of both deceased and living donor kidney transplant for all patients with end stage kidney disease. However, a relatively lower proportion of Indigenous Australians receive kidney transplant (Figure 1.1).

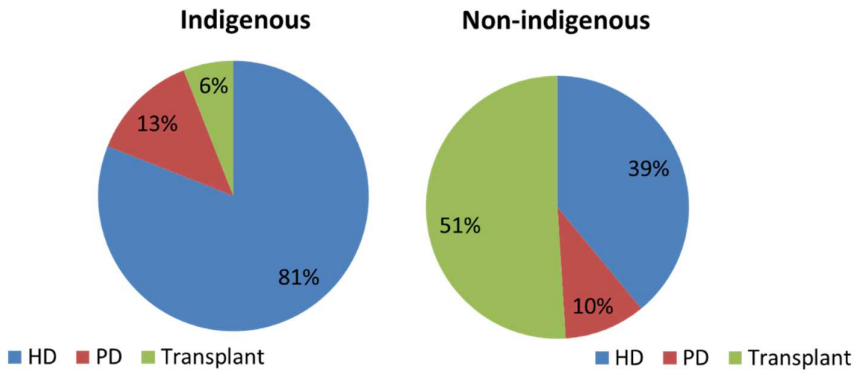

Figure 1.1: Prevalent patients on KRT by ethnicity for the year 2017

Furthermore, it is important to understand that in the process to receive kidney transplantation, patients must go through several steps (Figure 1.2), and be wait-listed. (10) Factors that affect the chance of kidney transplantation can be related to any of these steps, including placement on the transplant waiting list. In 2003, Cass et al. used Registry data to identify very low rates of placement on transplant waiting list among Australian Indigenous patients and proposed that this could be contributing to the low rates of transplants in this population. (11) However, this work was limited by the nature of the waiting list data collected by the Registry at that time; there were inaccuracies, from the fact that it was reported by renal units rather than from the actual waiting list database, and data lacked key details including dates of listing.

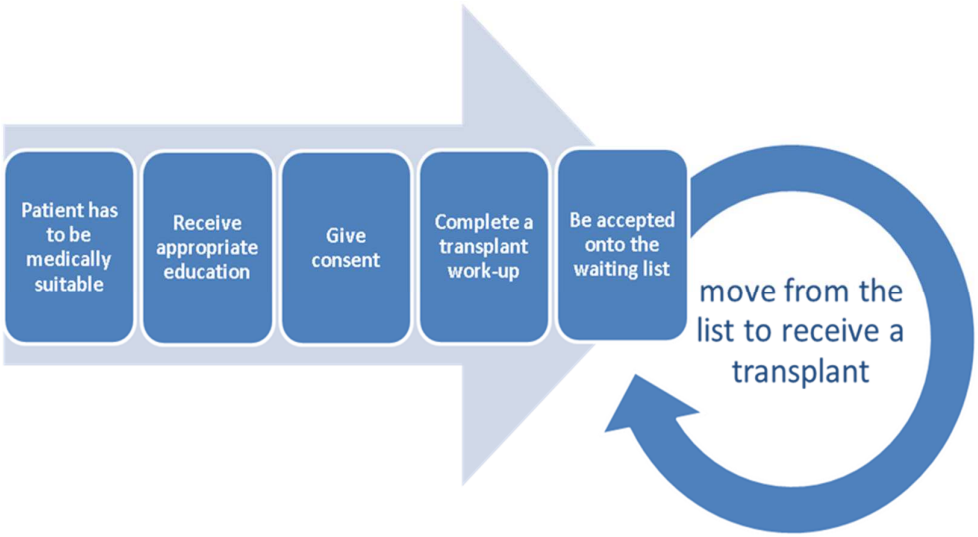

Figure 1.2: Process/ Pathway to receiving a kidney transplant

With the availability of the waiting list database (National Organ Matching System (NOMS)), which is more accurate and updated than the data examined by Cass et al.; it was necessary and possible to re-examine the activities on the kidney transplant waiting list for Indigenous patients. We expected to identify whether delayed or reduced placement on the transplant waiting list was associated with these low rates of a kidney transplant seen among Indigenous patients.

Besides, we examined the effect of patient-level information (dialysis attendance) on the access to the waiting list, kidney transplant and transplant outcomes.

Finally, kidney transplant outcomes (including graft loss and patient death) are poorer for Indigenous compared to non-indigenous Australians. (12) Even though previous studies (10, 13-16) have attempted to explore the reasons for the decreased proportion of kidney transplant and poor transplant outcomes among Indigenous ESKD patients, these studies were generally based solely on Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry data. However, this data lacks granular details at the patient level. We used a detailed examination of

hospital data to examine factors which affected transplant outcomes. We examined the effect of remoteness using multivariate regression and shared. Remoteness was defined by Australian Bureau of Statistics (ABS) remoteness categories, by linking ABS postcode of residence concordance data with the postcode recorded in the ANZDATA record for the start of RRT.

The specific aims of this these are:

- To identify the time to placement on the transplant waiting list and time to transplantation among Indigenous Australians as compared to non-indigenous Australians

- To examine predictors of placement on the transplant waiting list (and non-listing) for kidney transplantation utilising existing data from Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which holds waiting list data from the National Organ Matching System.

- To examine relationships between Indigenous patients' facility haemodialysis attendance and the chance of placement on the transplant waiting list, transplantation and transplant outcomes.

- To identify risk factors predictive of good vs poor outcome following transplantation among Indigenous recipients, through quantitative studies utilising existing ANZDATA Registry data

Implementation

The projects conducted will identify wherein the process of transplantation, do the problems lie. These findings will inform which part in the patients' journey to kidney transplantation need specific attention and where the changes in policies and

protocols are to be implemented. One of the studies will prove (or disprove) some of the factors thought to be associated with poor outcomes of the kidney transplantation. This finding will provide practitioners with an evidence base and is likely to affect the decision making for the process of transplantation, thereby removing assumption induced bias. Finally, identification of these factors and relationships will inform policymakers and clinicians to formulate strategies to improve access to and outcomes of kidney transplantation.

CHAPTER 1

Overview of access to kidney transplantation among Indigenous Australians

Issues around access to transplantation: The known

Factors predicting access to the kidney transplant waiting list and outcomes in Indigenous Australians may be divided into general factors which affect the overall health of Indigenous Australians, (17, 18) and kidney transplant specific factors.

General factors affecting the overall health outcomes of Indigenous Australians (17, 18)

Overall, health outcomes among Indigenous Australians are substantially poorer than among non-indigenous Australians. Life expectancy is 8.6 years less for males and 7.2 years less for females, (19) age-standardised hospital admission rates are 2.3 times higher, (20) and Indigenous Australians experience 7.3 times the burden of disease due to chronic kidney disease. (2)

Several factors contribute to these disparities:

Health system of the country- With health and vitality scores comparable to other member nations of Organisation for Economic Co-Operation and Development (OECD), Australia has one of the robust health systems in the world. (21) However, inequitable access to health services and health outcomes in Indigenous Australians are a major concern. (2)

The geography of Australia and limited infrastructure in remote areas means limited access to health care services. (22) Australia's remote and very remote areas are inhabited mainly by Indigenous Australians, these areas are thinly populated, and scattered over a big landmass. (23) According to the population census 2016, only one-third of Indigenous Australians lived in the major cities. Approximately 38% of Indigenous Australians lived in the outer-regional, remote and very remote areas. (23) People living in rural and remote areas face major health challenges. (22, 24) As the

distance from the major cities increases, levels of illness and mortality rates increase. (25) The fatal burden of disease, in general, is highest among Indigenous Australians residing in remote areas, (26) including disease burden due to kidney and urinary diseases. (2)

These issues of difficult geography and limited infrastructure are reflected in the prevalence of chronic kidney disease. Very remote areas had more than 6.0 times the rate of kidney & urinary diseases as compared to Major cities. (27) Hoy et al. reported 12.8 times more hospitalisations among Indigenous Australians from remote and very remote areas who had CKD compared to their non-indigenous counterparts. (28) In 2017-2018, the rate of hospitalisations among people living in very remote area was twice as high, and 1.3 times higher than for people living in remote areas. (29)

Indigenous Australians living in rural and remote areas have lower access to health services such as dentists, doctors, counsellors, health professionals and hospitals. (17, 29) According to a report by Hussain et al., many remote areas are dependent on visiting health professionals which leads to lack of continuity of care. (30) Fly in fly out (or drive in drive out) model of care is prone to frequent interruption in service delivery due to logistic issues. Flight cancellation and natural disasters are some examples. (30) Also, Alston M. highlighted an array of reasons associated with access to primary healthcare (PHC) services in rural Australia, contributing to health inequalities faced by the people residing in these areas. These include limited access to doctors and grossly inadequate access to specialists are to name a few. (22, 29, 31) In a report by Australian Institute of Health and Welfare, limited availability of specialised service and shortage of health professionals with the experience to work with complex ESKD patients or kidney transplant recipients was

proposed as a possible factor contributing to poor outcome seen in Indigenous Australians. (32) These issues in access of health services might lead to a delay in diagnosis and management of the medical conditions.

Similar issues in the context of complex medical conditions such as chronic kidney disease may exist. Whether they specifically affect onward referral to the kidney specialists and delay in initiation of specific treatment is not known but likely. Late referral of patients to the specialists is defined as a situation where kidney replacement therapy is required within 1-6 months of presentation to the specialists. Even though the registry-based data does not show a difference in the rate of late referral to kidney care between Indigenous and non-indigenous Australians, a late referral might be an issue among Indigenous patients from remote areas as compared to the major cities. Lim et al. reported a reduction in the occurrence of late referral in recent times, 25% in 2005 to 18% in 2017, thus still occurring 1 out of 5 Australians with ESKD. (33) Cass et al. reported late referral as one of the many reasons for the poor outcome of the patients with ESKD. Specifically, the late referral was associated with increased mortality and decreased access to a kidney transplant. (34, 35) Moreover, Smart et al. showed early referral to be associated with improved survival, reduced hospitalisation, early placement of arteriovenous fistula, better preparation for kidney replacement therapy, and better uptake of peritoneal dialysis. (36) The ANZDATA Registry reported that the proportion of arteriovenous fistula at dialysis start to be similar between Indigenous and non-indigenous Australians with ESKD. (4) However, the information on vascular access for dialysis at the start of KRT only reflects one aspect of comprehensive management of ESKD patients.

The problems related to remote residence continue after kidney transplants. Barraclough et al. showed increased rates of graft loss and patient death in Indigenous kidney transplant recipients from rural location compared to those from the urban area. (37)

From the above narrative, it is clear that the geography of Australia is contributory to the health disadvantage faced by Indigenous Australians residing in these areas. These issues of poor infrastructure and reduced access to healthcare services are further complicated by socioeconomic disadvantage, which is higher among Indigenous Australians living in rural and remote areas than those in major cities. (38)

Moreover, the poor health outcomes among Indigenous compared to non-indigenous Australians is also seen in people residing in urban and non-remote areas. Disparities are reflected in CKD associated hospitalisations, for which the rate ratio was 2.9 and 3.8 in Indigenous patients from major cities and inner regional areas, respectively. (28) Also, the age-standardised incidence rates of treated ESKD was higher among Indigenous Australians from urban areas compared to their non-indigenous counterparts. (39) These observations raise one important question:

'Are there factors which are common in both non-remote and remote areas which affect the health outcomes of Indigenous Australians? Are these health system-related or human-related and therefore "systemic racism" or "institutional racism"?'

Ketchell M. described "systemic racism", or "institutional racism", which refers to how ideas of white superiority are captured in everyday thinking at a systems-level, taking in the big picture of how society operates, rather than looking at one-on-one interactions. Systemic racism can stem from education, hiring practices or access,

including access to health service. (40) Bourke et al. quoted institutional racism to be a major contributor to the health gap between Indigenous and non-Indigenous Australians. (41) While the effect of remoteness remains significant, institutional racism might explain the remaining disparity in health outcomes seen among Indigenous Australians from the non-remote area. The same authors attributed 47% of the discrepancy on the health of Indigenous Australians to racism. (41) If such issues exist, then all Indigenous patients who come in contact with health service are likely to be affected, including Indigenous patients with ESKD. Despite the knowledge that institutional racism prevails, there is a paucity of data in this area. Ben et al. performed a systematic review and meta-analysis on racism and health service utilisation. They found a significant increase in research in this field in recent years; however, more than 95% of the studies reviewed were from the United States. As the saying goes

"You will never find the solution if you do not see the problem"- Gilbert K. Chesterton

Is this why there is a paucity of research on Institutional racism from Australia? Is this why from 1965 (Convention on the Elimination of All Forms of Racial Discrimination was opened for signature on 21 December 1965) to 2020 we have failed to close the health gap between Indigenous and non-indigenous Australians? (42) The research studies conducted for this thesis have taken into consideration all factors which were possible to be examined by the quantitative methods. Examining the effect of institutional racism was beyond the scope of this thesis. However, by accounting for all other factors possible to be associated with poor outcomes among Indigenous Australians with ESKD, it may be implied that a significant proportion of unmeasured residual factor found to contribute to the discrepancy in our studies might be due to institutional racism.

Besides, there are other possible risk factors (discussed in the following section) which may be attributed to the disparity in the health outcomes, including outcomes related to kidney disease, between Indigenous and non-Indigenous Australians and may exist in Indigenous Australians from both remote and non-remote areas.

Additional possible risk factors for poor kidney health outcomes of Indigenous Australians

The factors which might play a role in determining the disparity in the health outcomes may be divided as A. modifiable and B. non-modifiable. These factors which contribute to the disparity in health outcomes will also be associated with the outcomes related to kidney disease among Indigenous patients.

A. Modifiable factors include health behaviours, infectious diseases, and household, social and environmental factors
B. Non-modifiable (or relatively non-modifiable) factors include genetic predisposition to the disease, gender and age

There is an increased prevalence of comorbidities (such as diabetes, cardiovascular disease, cerebrovascular disease, and peripheral vascular disease) smoking and obesity in Indigenous Australians. (39) Furthermore, the prevalence of these factors is higher in the Indigenous population living in the socially-disadvantaged region, at a younger age, and the severity of illness is higher than their non-indigenous counterparts. (39) This increased rate of chronic disease may explain the increased rate of CKD and ESKD in the Indigenous population. Moreover, obesity, diabetes and chronic kidney disease are associated with a physical disability and increased rates of hospitalisation. (43, 44) This adds to increased years of life lost due to chronic conditions (27, 44) and contributes to more premature death in young Indigenous Australians. Death rates at age 55-64 are ten times higher when compared to non-Indigenous Australians. (2)

Also, there are increased rates of childhood infection in this group, such as acute rheumatic fever, skin infections, and diarrhoeal illness. Geographic and

environmental factors described before (poor sanitation, decreased access to fresh foods, overcrowding) also leads to increased rates of infection (17, 27, 39). Frequent such insults may affect the kidneys (for example by acute kidney injury, post-infectious glomerulonephritis) which can precipitate and aggravate CKD.

Infection also possesses a major issue in Indigenous transplant recipients. Barraclough et al. (15) reported the excess of infectious deaths in Indigenous recipients living in urban locations. Rogers et al. (14) examined the transplant recipients of the NT and found infection to be the most common reason for graft loss among Indigenous transplant recipients of the region. With 40% of the NT population residing in remote and very remote areas, Rogers study can be interpreted as that the infection-related morbidity and mortality is also common in Indigenous transplant recipients from rural areas. (23)

Barraclough et al. also proposed a variation in immunosuppressive drug disposition due to racial differences as another explanation of graft loss among Indigenous transplant recipients. (45) However, this has not been formally examined.

Finally, in a coronial series of seventeen Aboriginal and twenty-four non-Aboriginal people, investigators found that decreased nephron mass was more common in Aboriginal Australians. There was a trend of hypertension and low birth weight among the study participants, and reduced nephron number was associated with glomerulomegaly. (46, 47) It may be argued that perhaps, a kidney with glomerulomegaly and hyperfiltration will be less able to withstand further insults from hypertension, diabetes or infection and thus lead to rapid progression to CKD and ESKD. Bertram (48) and Hoy (49) identified low birth weight, maternal smoking, and poor nutrition causing decreased nephron mass as independent factors contributing

to the increased prevalence of hypertension, CKD and rapid progression to ESKD. (48, 49) There are studies underway to identify risk factors which may be genetically driven. Whether the problems of reduced nephron numbers, glomerulomegaly and hyperfiltration are genetically linked among Indigenous Australians remains to be examined.

In the sections and chapters to follow, studies conducted in fulfilment of this thesis are presented. Through our research, we have attempted to add to a better understanding of the risk factors focusing more on those that contribute to decreased access to the best available treatment for Indigenous Australians with ESKD (i.e. kidney transplantation).

Before delving into the transplant specific access related issues, it is important to understand the current demography of ESKD among Indigenous Australians. The enclosed publication (50) provides an overview of KRT in Indigenous Australians with ESKD compared to non-indigenous Australians; this is followed by a brief overview of kidney transplantation among Indigenous patients.

Statement of Authorship

Title of Paper	Overview of dialysis in indigenous compared to nonindigenous Australians
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	©2016 Dustri-Verlag Dr. K. Feistle ISSN 0301-04305S DOI 10.5414/CNP86S119, e-pub: July 29, 2016

Principal Author

Name of Principal Author (Candidate)	Namrata Khanal		
Contribution to the Paper	Literature review, data analyses, manuscript writing, all steps in the process of publication in the journal		
Overall percentage (%)	100		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/05/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Philip Clayton		
Contribution to the Paper	Supervising data analyses, manuscript writing and editing		
Signature		Date	1/6/20

Name of Co-Author	Stephen McDonald
Contribution to the Paper	Manuscript writing and editing

Signature		Date	1/6/2020

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Name of Co-Author	Matthew Jose		
Contribution to the Paper	Manuscript writing and editing		
Signature		Date	30/05/2020

clinical nephrology

ISSN 0301-04305S

DOI 10.5414/CNP86S119
e-pub: July 29, 2016

Overview of dialysis in indigenous compared to nonindigenous Australians

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Key words
renal replacement therapy – indigenous Australians – end-stage kidney disease

Abstract. Introduction: Indigenous Australians (Aboriginal and Torres Strait Islanders, ATSI) make up 3% of the total Australian population [1] and comprised ~ 10% of new patients beginning renal replacement for end-stage kidney disease (ESKD) in Australia during 2013 [2]. In this study, we examined the differences in characteristics, incidence, and prevalence of different modalities of dialysis and survival between indigenous and nonindigenous Australians. Methods: We examined outcomes of all adults (aged ≥ 18 years at the start of renal replacement therapy (RRT)) in the ANZDATA registry who started RRT from 1st Jan 2003 to 31st Dec 2013 in Australia. Adjusted patient survival on dialysis was calculated using standard techniques. Results: A total of 25,528 participants were included, of whom 2,447 (9.5%) were indigenous Australians. Use of facility hemodialysis was more common among indigenous people, odds ratio (OR) 1.79 (95% confidence interval (CI), 1.37, 2.35). Of several interactions between indigenous status and other comorbidities, the most clinically significant was one with diabetes. In fully adjusted models, compared to nonindigenous with diabetes; death risk was higher for indigenous people with diabetes, HR 1.15 (95% CI, 1.06, 1.25). There was no difference between the two groups without diabetes, HR 0.86 (95% CI, 0.73, 1.05). There was no variation in the risks associated with ethnicity over year of dialysis start. Conclusion: There are differences in adjusted outcomes of indigenous Australians compared to nonindigenous with ESKD. Interactions suggest that the influence of reported comorbidities may differ in this group. Further investigations will be valuable in closing the gap and improving health outcome of indigenous Australians on RRT.

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Introduction

The incidence of treated end-stage kidney disease in indigenous Australians (Aboriginal and Torres Strait Islanders) is 10 times higher for males and 15 times higher for females aged 35 – 64 years than for nonindigenous people [2]. Indigenous Australians make up 3% of the total Australian population [3] and comprise ~ 10% of new patients beginning renal replacement for end-stage kidney disease (ESKD) [2].

A recent publication [4] showed no improvement in the gap in outcomes between indigenous and nonindigenous Australians with ESKD between 1995 and 2009. In 2008, the Council of Australian Governments agreed to address the disadvantage faced by indigenous Australians and "close the gap" in indigenous people's health outcomes, in addition to other targets [5]. We extended and updated this comparison of indigenous Australians with nonindigenous Australians' outcomes to include the participants who were treated with dialysis modalities (hemodialysis and peritoneal dialysis but not renal transplantation) until the end of the year 2013, following implementation of targeted programs at the national level [5].

Methods

Description of cohort and inclusion criteria

All adults (≥ 18 years at start of renal replacement therapy (RRT)) who started renal replacement in Australia during the period from 1st Jan 2003 to 31st Dec 2013 were included. Indigenous origin is recorded in ANZDATA registry as reported by the renal unit on the basis of self-description. 44 records were excluded due to inability to link post-

codes to those recorded by the Australian Bureau of Statistics (ABS). The study cohort was divided in two categories: indigenous Australians (comprising Aboriginal and Torres Strait Islanders) and nonindigenous Australians.

Statistical analysis

Outcome

Distribution of RRT modality and all-cause mortality following start of RRT in indigenous and nonindigenous Australians were the outcome measures.

Baseline characteristics

Comparisons of comorbidities used Wilcoxon's signed rank test and Pearson's χ^2 as appropriate.

Remoteness

Remoteness was measured by matching the postcode at the start of RRT to remoteness concordance tables from the ABS [6]. There are five remoteness categories: 1) Major cities of Australia; 2) Inner Regional Australia; 3) Outer Regional Australia; 4) Remote Australia; 5) Very Remote Australia. Sensitivity analyses were carried out to assess the association and effect of remoteness on the outcome.

Distribution of RRT modality

Comparison was also made between the incident modality at the start of RRT and prevalence of each modality of RRT at 90 days, 6 months, and 12 months from the start of RRT. The distribution of RRT modality was also assessed across the remoteness categories.

Survival analysis

Patient survival on RRT was calculated and compared between the two groups using Cox regression model adjusting for the confounding factors at commencement of renal replacement therapy: age, gender, body mass index (BMI) category (< 18.5, 18.5 – 24.9, 25 – 29.9 and > 30 kg/m^2), smoking status, diabetes, comorbidities (chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease), primary kidney disease, late referral (commencing renal replacement therapy within 3 months of referral to nephrology care), and remoteness. Comorbidities reported as "yes" and "suspected" were combined as "yes". To investigate the change in outcome over the years, year of RRT start was categorized as 2003 – 2006, 2007 – 2009, and 2010 – 2013.

Given the small number of participants in each group, type 1 diabetes was combined with type 2 diabetes, and participants in remote categories inner regional, outer regional, remote, and very remote Australia were grouped together to improve statistical power. Interactions (between indigenous status and each of: age at RRT initiation, diabetes, chronic lung disease, and coronary artery disease, remoteness) were tested using Wald tests. Only significant interactions were included in the final regression model. Survival time was the time a patient started on renal replacement therapy until the event (death) occurred. Data was censored at the end of the survey on 31st December 2013, first transplant, and recovery of renal function or loss to follow up. Odds and hazard ratios were calculated and presented with 95% confidence intervals (CI), and a p-value of < 0.05 was used as the indicator of statistical significance. Statistical analysis used Stata version 14.1 (StataCorp LP, College Station, TX, USA).

Ethical considerations

Analyses were performed on a deidentified data extract.

Results

Baseline characteristics

There were 25,528 participants, of whom 9.5% (n = 2,447) were Indigenous Australians. There were higher proportion of indigenous female participants (n = 1,351, 55.2%) as compared to males (n = 1,096, 44.8%), and comorbidities were more common in this group.

Table 1. Baseline characteristics of participants at entry by hemodialysis (HD) and peritoneal dialysis (PD) (Not included in the table are those in the home-HD group and pre-emptive transplant. There were no indigenous participants in the home-HD group at entry, and only 3 indigenous participants had received pre-emptive renal transplant).

RRT modality	Facility HD*		Peritoneal dialysis*	
Ethnicity	Nonindigenous	Indigenous people	Nonindigenous	Indigenous people
N	16,522	2,048	5,664	396
Age at RRT initiation, median (IQR)	65.0 (54.0, 75.0)	51.0 (43.0, 59.0)	63.0 (51.0, 73.0)	52.0 (44.5, 61.0)
Females	5,974 (36.2%)	1,134 (55.4%)	2,348 (41.5%)	215 (54.3%)
Males	10,548 (63.8%)	914 (44.6%)	3,316 (58.5%)	181 (45.7%)
Body Mass Index (kg/m^2)				
< 18.5 (underweight)	523 (3.2%)	71 (3.5%)	183 (3.2%)	10 (2.6%)
18.5 – 24.9 (normal)	5,435 (33.3%)	606 (30.0%)	2,049 (36.4%)	111 (28.5%)
25 – 29.9 (overweight)	5,161 (31.6%)	578 (28.7%)	2,005 (35.6%)	131 (33.6%)
≥ 30 (obese)	5,200 (31.9%)	762 (37.8%)	1,399 (24.8%)	138 (35.4%)
Comorbidity				
Chronic lung disease	3,005 (18.2%)	401 (19.6%)	774 (13.7%)	68 (17.2%)
Diabetes (type 1 or type 2)	7,061 (42.7%)	1,669 (81.5%)	2,259 (39.9%)	297 (75.0%)
Peripheral vascular disease	4,552 (27.6%)	591 (28.9%)	1,213 (21.4%)	127 (32.1%)
Coronary artery disease	7,322 (44.3%)	869 (42.4%)	1,957 (34.6%)	177 (44.7%)
Cerebrovascular disease	2,663 (16.1%)	243 (11.9%)	794 (14.0%)	57 (14.4%)
Late referral	4,353 (26.4%)	616 (30.5%)	732 (13.0%)	71 (18.1%)
Primary renal disease				
GN	3,719 (22.5%)	255 (12.5%)	1,461 (25.8%)	61 (15.4%)
Polycystic	1,040 (6.3%)	6 (0.3%)	423 (7.5%)	4 (1.0%)
Reflux	380 (2.3%)	31(1.5%)	190 (3.4%)	7 (1.8%)
Hypertension	2,632 (15.9%)	146 (7.1%)	857 (15.1%)	28 (7.1%)
Diabetes	5,105 (30.9%)	1,416 (69.1%)	1,711 (30.2%)	259 (65.4%)
Other	3,646 (22.1%)	194 (9.5%)	1,022 (18.0%)	37 (9.3%)
Remoteness				
Major cities	12,071 (73.1%)	304 (14.8%)	3,967 (70.0%)	62 (15.7%)
Inner regional	3,014 (18.2%)	200 (9.8%)	1,053 (18.6%)	39 (9.8%)
Outer regional	1,260 (7.6%)	529 (25.8%)	536 (9.5%)	118 (29.8%)
Remote-VRA¶	150 (0.9%)	1,013 (49.5%)	103 (1.8%)	177 (44.7%)

*RRT modality at entry; ¶Very remote Australia (VRA); participants from remote and very remote Australia combined. RRT = renal replacement therapy; IQR = interquartile range; GN = glomerular nephritis.

Mean BMI was similar in indigenous people compared to nonindigenous, 28.0 kg/m^2 (95% CI, 28.4, 29.0) vs. 27.0 kg/m^2 (95% CI, 27.6, 27.8), respectively.

Overall, nonindigenous participants in the study were predominantly from Major Cities of Australia (72.7%), compared to indigenous participants (15.2%). Larger proportions of indigenous participants were from postcodes corresponding to outer regional Australia (31.4%), remote (22.4%), and very remote Australia (21.1%), p-value < 0.001(Pearson's χ^2).

Of the RRT modalities, facility hemodialysis was the main modality of RRT; odds ratio (OR) for facility HD in indigenous (compared with nonindigenous) participants at initiation of RRT was 1.79 (95% CI, 1.37, 2.35). This OR increased to 2.19 (95% CI, 1.76, 2.74) at 12 months from RRT start. The point prevalence at 12 months since RRT start for the use of peritoneal dialysis and home hemodialysis was significantly lower among indigenous participants, OR 0.62 (95% CI, 0.47, 0.81) and 0.42 (95% CI, 0.21, 0.86), respectively. Remoteness was not associated with the use of any of the modalities of RRT in the indigenous participants. In both groups, the proportion of people receiving home-based treatment decreased over time. Table 1 illustrates the baseline characteristics of participants on hemodialysis and peritoneal dialysis at RRT start.

Patient survival

Unadjusted cumulative mortality (Figure 1) for indigenous participants on dialysis was

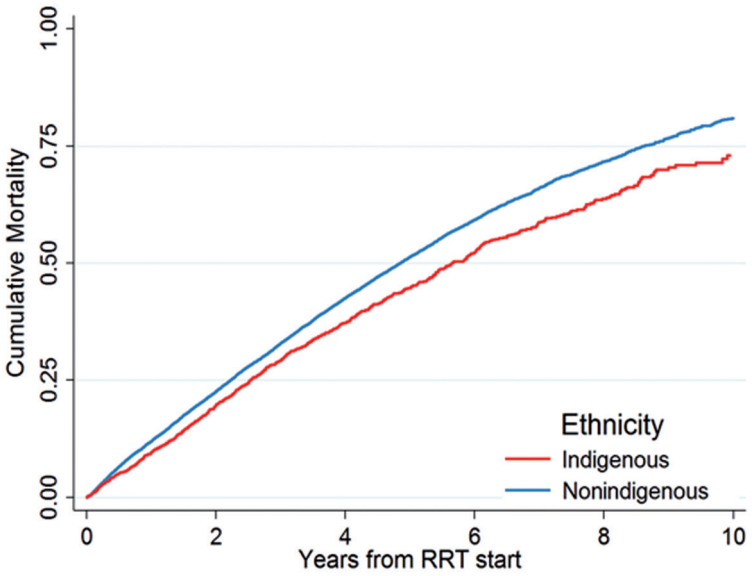

Figure 1. Unadjusted cumulative mortality by ethnicity. (However, the risk of death was higher for indigenous people with diabetes compared to their nonindigenous counterparts. Please refer to the text for further details on adjusted HR and significant interactions).

lower compared to nonindigenous Australians (hazard ratio (HR) for death 0.83 (95% CI, 0.8, 0.9)), p-value < 0.001. There were statistically significant interactions between indigenous status and each of the following factors: age at RRT initiation, diabetes, coronary artery disease, chronic lung disease, and peripheral vascular disease. In general, these interactions were not clinically meaningful, with the exception of diabetes. There was no difference in adjusted survival for indigenous and nonindigenous participants without diabetes. The risk of death was higher for indigenous people with diabetes compared to their nonindigenous counterparts, HR 1.15 (95% CI, 1.06, 1.25), p-value < 0.05. However, the hazard ratio for death for indigenous without diabetes compared to their nonindigenous counterparts was 0.88 (95% CI, 0.73, 1.05).

Discussion

We have demonstrated a number of important differences between indigenous and nonindigenous people receiving dialysis in Australia. Overall, indigenous participants were younger but had a substantially higher prevalence of comorbidities. Indigenous people were predominantly from outside major cities of Australia and were treated with facility hemodialysis. Despite increased efforts to increase the availability of nursing and home therapy support outside major cities [7], disparities in the use of home dialysis modalities continue. There are considerably greater training and logistic challenges for home hemodialysis, particularly in areas where water and electricity supplies are not reliable [8]. Decreasing use of peritoneal dialysis may in addition be due to increased rates of peritonitis and technique failure in the indigenous group, as has been reported previously [9]. Eventually, this may lead to technique failure and change in modality [9]. While dialysis modality may have an effect on survival [10], this was beyond the scope of our analysis.

The differences in outcome between indigenous and nonindigenous people were dependent on diabetes – in those without diabetes we did not observe a difference. However, among participants with diabetes, there was a difference in risk associated with indigenous status. We observed no difference in the risks associated with ethnicity over year of dialysis start in our study. At a practical level, this extends the findings from a previous study [4] of no improvement (over 2005 – 2009) despite new and ongoing programs to address indigenous health and extend service provision.

The standardized death rate according to the Australian Bureau of Statistics for indigenous people is 9.8 as compared to 5.5 per 1,000 standard population for nonindigenous [1, 6]. Thus, in addition to the factors associated with dialysis and measured comorbidities, there may be other unmeasured factors, like socioeconomic condition and social disadvantage, influencing the difference.

The interactions observed are challenging to interpret. To improve the statistical power, we have restricted the analysis to include significant interactions and collapsed multiple categories (remoteness, diabetes, comorbidities, and primary renal disease) to binary covariates. The Registry does not collect information about the severity of comorbidities; one explanation for the interaction observed would be if diabetes were more severe or more likely to be associated with complications among indigenous people. Reporting bias is also a possible factor.

Our study has several strengths, which include the large inclusive cohorts of patients and the consistent adjustment for relevant clinical variables including remoteness. There are a number of areas where our analyses can be developed. Some are outlined above, others include methodological developments (for example competing risk methodologies to account for differential transplant rates), and teasing apart remoteness and socioeconomic status. Ongoing work will be required to tease out further interactions.

Conclusion

Even though overall survival was seen to be improving over more recent years, the excess risk of death associated with indigenous status has not improved. Remoteness continues to be an important factor in predicting death risk in indigenous participants. Indigenous origin appears to play a particular role in modifying the risk associated with diabetes. This is a complex issue and requires further investigations to identify these predictors in closing the gap and improving health outcomes of indigenous people with ESKD.

Acknowledgment

The authors would like to acknowledge the substantial contributions of the entire Australian and New Zealand nephrology community (physicians, surgeons, database managers, nurses, renal technicians, and patients), who provide information to and maintain the ANZDATA database. We would also like to acknowledge and extend our gratitude to the Australia and New Zealand Dialysis and Transplant registry.

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A brief overview of kidney transplantation in the context of Australia and Indigenous Australians is presented here.

Although the rate of kidney transplantation has increased in recent years, Indigenous Australians made up only 3% of transplant recipients in 2017. (51) In 2017, of the prevalent Indigenous patients, only 13% were treated with kidney transplants (Figure 1.1, page 10). (12) Figure 1.3 shows the prevalent Indigenous transplant patients by Australian state and territory for the years 2013 to 2017. (12)

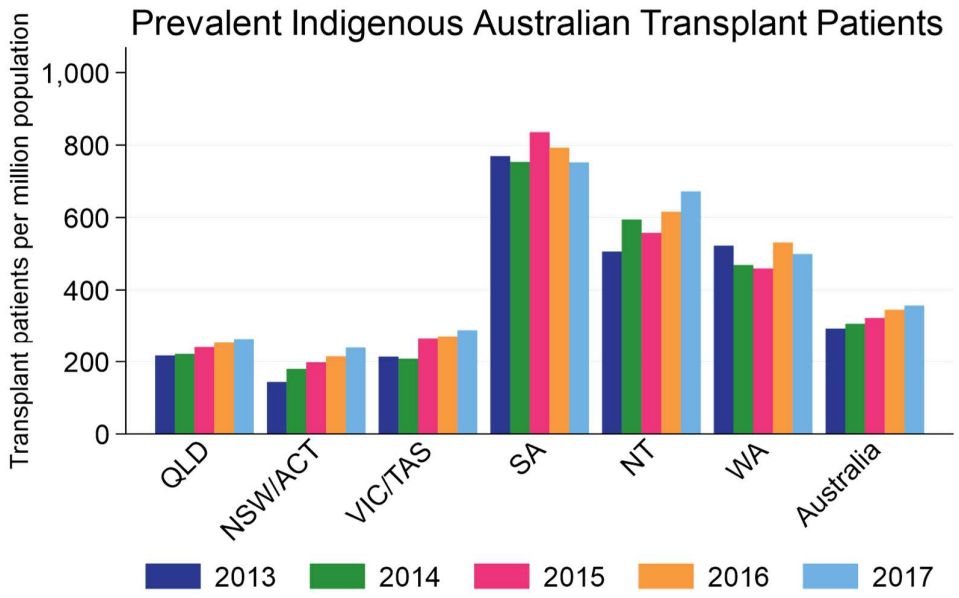


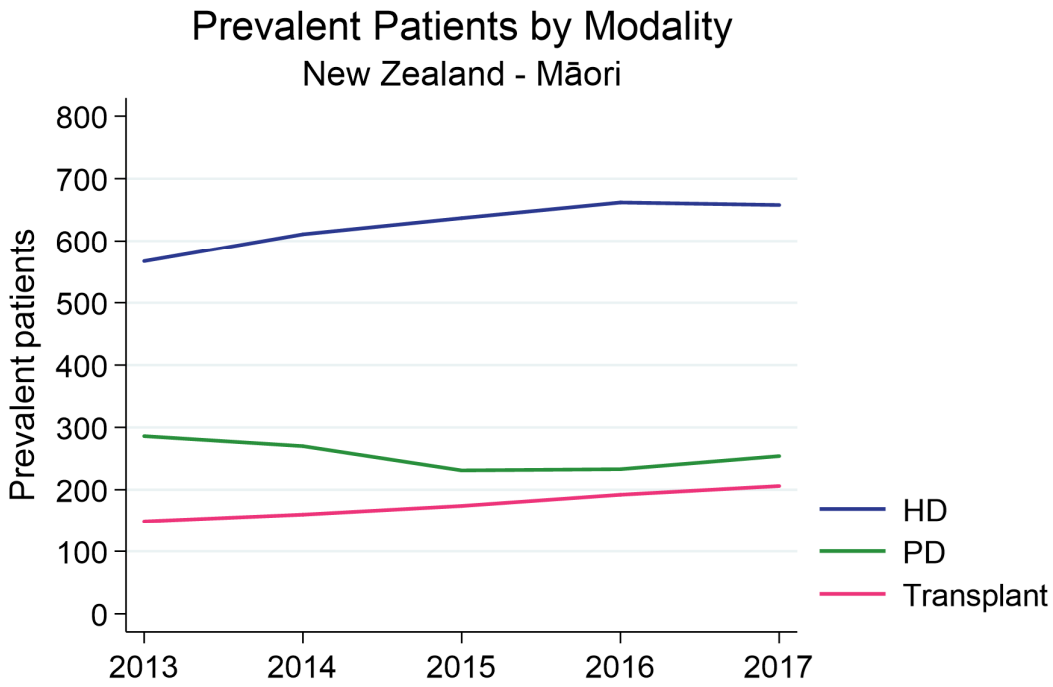
Figure 1.3: Prevalent Indigenous Australian transplant patients

Similar issues affect other First Nations people and other ethnically disadvantaged groups. New Zealand (NZ) Māori and Pacific Island people (from countries like Samoa, Tonga, Niue, Fiji, Tuvalu, Vanuatu, Nauru, the Marshall Islands, and the Solomon Islands) continue to experience worse socioeconomic and health outcomes compared with those of other ethnicities. These health inequalities include kidney disease. (52) Inequities are seen across multiple mortality and morbidity indicators (e.g. communicable diseases, mental health, and chronic diseases). (53)

End-stage kidney disease in Indigenous population: International context

New Zealand

Being NZ Māori is one of the risk factors for kidney disease on the list provided by the NZ Ministry of Health. (54) In 2017, 30% of all patients starting KRT in New Zealand were Māori and an overall prevalence of 57% of the New Zealand dialysis population. (12) Incident haemodialysis commencement was four-fold higher for Māori and Pacific people. (12) Among people aged less than 60 years at KRT start, in 2013, 71% of surviving non-Māori, non-Pacific New Zealanders had received a kidney transplant by five years compared with 26% of Māori and 25% of Pacific people. (55) While a constant increase in the numbers of kidney transplant was seen for Māori and Pacific people in the year 2013 to 2017 (Figure 1.4), an incident pre-emptive kidney transplant was 17 fold lower for NZ Māori in 2017. (12)



2018 ANZDATA Annual Report, Figure 10.9.1

Figure 1.4: Prevalent New Zealand Māori patients by modality

There is increased mortality in the immediate post-transplantation period, and then the graft survival was comparable to non-Maori, non-Pacific people in the first three years for the Maori people. Pacific people have an increased rate of graft loss after 18 months of transplantation. (12) Non-related live donor transplants have increased for this group of people in recent years.

Canada

Indigenous Australians of Canada include First Nations, Inuit, and Métis people. They constituted 4.9% of the total population of Canada, according to the 2016 Canadian census. (56) Indigenous Canadians have a disproportionately high burden of ESKD requiring dialysis and transplantation and are suggested to be driven by the lack of appropriate pre-dialysis care. (57, 58) Experts suggest the imminent need to understand the disparities and the reasons for its existence. (59) Underutilisation of self-care treatment options has been frequently reported among Aboriginal Canadians. (60-62) Geographic distance to the treatment providing centre has been thought to play a role in the selection of self-care treatment modality by the Aboriginal Canadians. (63) One study which involved three study sites and surveyed 99 aboriginal patients reported anxiety and financial issues are perceived as barriers to peritoneal dialysis by the Aboriginal Canadians. It is suggested that shared decision making between the treating physician and the patient may help address this issue. (64)

United States

As per July 2018 census, the Native Americans (American Indians and Alaskan natives) made up 1.3% of the total population of America. (65) Historically, the American Indians and Alaskan natives have the highest rates of kidney disease, (66) specifically diabetes-related kidney disease. In recent years, with improved diabetes management among Native Americans, end-stage kidney disease has declined significantly. (67) The crude transplant rate was more than two-fold higher for the white Americans, according to the study published in 2009. (13) Transplant rate has changed in recent years by almost 50%. The rate of transplant in the Native Americans was 2.8 compared to 3.9 per 100 dialysis patients among White

Americans in 2017 as per the United States Renal Data System (USRDS) annual report. (68)

Other parts of the world

Disadvantaged communities, those from low resource, racial and ethnic minorities, or indigenous backgrounds, suffer from marked increases in the incidence, prevalence, and complications of CKD worldwide. (69) Various poverty-related factors, e.g. infectious diseases secondary to poor sanitation, low birth weight, inadequate supply of safe water, environmental pollutants, and high concentrations of disease-transmitting vectors play an important role.

Summary- Putting above discussion and review into perspective for Indigenous patients with ESKD:

Indigenous Australians face a major disadvantage due to their geographical location. The unavailability of specialised service and infrastructure such as facilities for haemodialysis and specialist services required to manage patients with kidney transplants in remote areas limits management of ESKD patients closer to home. This leads to displacement, which gives rise to multiple psychosocial issues which contribute to poorer health outcomes. (70) It would be ideal to manage people from remote and very remote areas with home dialysis (home haemo- or peritoneal dialysis) and transplants. However, Lim et al. highlighted factors like logistic and technical issues, increased rates of peritonitis, technique failure, and peritoneal dialysis-related mortality in remote areas which make this difficult. (71) Furthermore, the same authors attributed significant travel distance leading to a lack of appropriate health services within easy access and when needed and poor attendance for specialist review, to these discrepancies. (71) A combination of these factors may explain the high proportions of Indigenous Australians being treated with facility

haemodialysis, as shown in our study. (50) While a service like that of a mobile dialysis unit addresses some of these problems, (72) management of ESKD patients with kidney transplant will be more definitive to keep people in their community. Compared to dialysis, it is cost-effective and improves the quality of life of the recipients. In the following section, we will learn about the specific factors affecting access to the kidney transplant.

Factors affecting access to treatment of kidney disease- Kidney transplant specific factors including waiting list

In previous sections, the general factors that contributed to health disparity faced by Indigenous Australians were discussed. The factors which are specific to Indigenous patients receiving dialysis and in particular, relating to access to and outcomes of kidney transplantation will be discussed here. These factors may be divided into:

<u>Known factors which potentially predict access to the waiting list and kidney transplant outcomes</u>

Known factors which potentially predict access to a waiting list and kidney transplant outcomes are outlined here. Cass et al. examined the registry-based data for ESKD patients from 1993 to 1998 and reported that Indigenous recipients wait longer on the waiting list. (11) The same authors also reported a decreased rate of transplantation after placement on the transplant waiting list among Indigenous Australians. (11) The longer time spent on dialysis potentially increases the morbidity and mortality, thereby decreasing patients' likelihood of receiving transplants. (9, 73) Furthermore, Indigenous recipients have a greater number of human leukocyte antigen (HLA) mismatches and greater sensitisation. (14, 74, 75) The differences in HLA distribution between donor and recipient pools might affect waiting times.

Previous studies (14, 37) have explored the effects of comorbidities and remoteness on kidney transplant outcomes. Compared to their non-indigenous counterparts, comorbidities are more common among Indigenous Australians before transplantation. These factors are important determinants of outcome, particularly patient survival; however, only partially explain the disadvantage faced by Indigenous Australians.

Living related kidney transplant could be an alternative to deceased donor transplantation. However, higher rates of CKD, diabetes and cardiovascular comorbidities in Indigenous Australians precludes family and friends from the donation. Previous studies have shown a higher rate of CKD (39) and the risk of developing severe kidney disease after donation. (76) In these circumstances, Indigenous Australians have to be highly dependent on the scarce deceased donor pool.

Proposed factors associated with poor access to the waiting list and kidney transplant:

As discussed in the previous section (please refer to page 12), to be placed on a waiting list and be considered for a kidney transplant, one has to go through several steps shown in Figure 1.2 (please refer to page 12). (10, 77) Difficulties faced at any of these steps shown in Figure 1.2 can become barriers to access waiting list and then kidney transplantation, leading to inequalities.

For some of these steps, patients are required to travel to a specialist centre where there is transplanting facility, and for others, to a regional hospital where a specialist may be visiting for pre-transplant assessment. This process often requires multiple and frequent trips to and from the centre. As discussed in chapter 1, Indigenous Australians from remote and very remote areas frequently face dislocation from their communities to access dialysis. For them, further travel to a regional centre frequently to be reviewed by a specialist can be very tiring physically as well as emotionally. This not only leads to a delay in the process but can increase the likelihood of people not attending their appointments. It is not just the distance one has to cover, but the expense related to the travel, accommodation of the

companion, isolation and having to confront unfamiliar or unwelcoming hospital environments might often be overwhelming. (78, 79) Similar challenges are faced by Indigenous Australians accessing other healthcare services besides kidney care, and also Indigenous people in other parts of the world. Lawrence et al. (80) and Katzenellenbogen et al. (81) identified fear of hospitals among Indigenous Australians with acute coronary syndrome. Indigenous Australians in their studies perceived hospitals as places to go to die or environment being unfriendly, and recognised these as a barrier to treatment of acute coronary syndrome. (80, 81) Alexander and Sehgal analysed the disparities in access to kidney transplant waiting list in Kentucky, Ohio and Indiana. (82) They concluded that pre-transplant evaluation which often requires multiple evaluations and frequent visits for sophisticated tests, posed the greatest barrier for ethnic minorities.

Patient's chance of being placed on the transplant waiting list is dependent on whether or not they are referred for pre-transplant assessment and placement on the transplant waiting list by their treating physicians. Cass et al. (83) and Anderson et al. (84) conducted studies to investigate physicians' attitude and its effect on access to transplantation. These studies (83, 84) highlighted that practitioners based their decision-making on patients' suitability for transplantation and transplant referral on clinical and behavioural factors. Cass et al. suggested that these factors cluster with ethnicity and are likely to contribute to poor access to transplantation. (83) Anderson et al. examined the effect of the treatment compliance, which comprised of frequent non-attendance in dialysis sessions, clinic reviews, improper medicine utilisation, all resulting in blood results unacceptable for a patient on dialysis and therefore poor health and increased hospitalisation. (84) The same authors reported that some of the Australian Nephrologists who responded to their survey were concerned about

the compliance with management among Indigenous Australians while on dialysis. They concluded that such concern regarding compliance seemed to play some role in referring these patients for pre-transplant workup. (84) More recently, Barraclough et al. (37) also confirmed the notion of poor compliance and poor outcome.

From the discussion above, we can synthesise the questions listed below.

- What are the additional factors which predict placement on the transplant waiting list (and non-listing) on the waitlist for kidney transplantation among Indigenous Australians
- Are there any associations between compliance with dialysis, hospitalisation and other markers of engagement with the health system during haemodialysis and the chance of placement on the transplant waiting list, transplantation and transplant outcomes?

Chapter 2 presents the publication which examined the effect of traditional predictors, including comorbidities and remoteness on the rates of placement on the transplant waiting list and kidney transplantation. The effect of dialysis attendance on placement on the transplant waiting list, kidney transplantation and outcomes among Indigenous patients with ESKD is examined in chapter 3. Chapter 4 includes two research studies which originated from a cohort of Indigenous kidney transplant recipients over a decade in an attempt to identify predictors of early graft loss, including hospital-based data.

CHAPTER 2

Access to the waiting list and kidney transplantation in current times

In the process to identify factors influencing the placement on transplant waiting list among Indigenous Australians with ESKD, the chance of placement on transplant waiting list information was examined using the most accurate data available. This section includes the research publication which addressed the following two aims.

1. To identify the time to placement on transplant waiting list and time to transplantation in Indigenous Australians as compared to the non-indigenous Australians.
2. To examine predictors of listing (and non-listing) on the waitlist for kidney transplantation utilising existing data (from the ANZDATA (Australia and New Zealand Dialysis and Transplant Registry), which holds waitlist data from the National Organ Matching System).

Statement of Authorship

Title of Paper	Disparity of access to kidney transplantation by Indigenous and non-Indigenous Australians
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Medical journal of Australia, first published 17 September 2018, doi: 10.5694/mja18.00304

Principal Author

Name of Principal Author (Candidate)	Namrata Khanal		
Contribution to the Paper	Literature review, ethics application, data analyses, manuscript writing, all steps in publication (submission to the journal, responses to the reviewers' comments), speaking to the media		
Overall percentage (%)	100%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/05/2020

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	01/06/2020

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Contribution to the Paper	Manuscript writing, review and editing		
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Name of Co-Author	Stephen McDonald		
Contribution to the Paper	Statistical analyses supervision, Manuscript writing, review and editing, speaking to the media		
Signature		Date	1/6/2020

Disparity of access to kidney transplantation by Indigenous and non-Indigenous Australians

Namrata Khanal[1,2], Paul D Lawton[3], Alan Cass[3], Stephen P McDonald[1,2,4]

The known Indigenous Australians with end-stage kidney disease are less likely to receive a kidney transplant than non-Indigenous Australians, and those who undergo transplantation have waited longer for a donor organ.

The new Indigenous patients were less likely than non-Indigenous patients to be added to the transplantation waiting list during the first year of renal replacement therapy; this disparity was not explained by differences in patient- and disease-related factors. The likelihood of transplantation during the first year of wait-listing was similar for both groups, but significantly lower for Indigenous patients in subsequent years. There are probably unmeasured confounding factors that influence wait-listing and transplantation rates.

The implications Changes in policy and practice are needed to improve the access of Indigenous patients to kidney transplantation.

Abstract

Objective: To compare the likelihood of Indigenous and non-Indigenous Australians being placed on the waiting list for transplantation of a kidney from a deceased donor; to compare the subsequent likelihood of transplantation.

Design, setting and participants: Observational cohort study; analysis of data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry for patients aged 18–60 years at the start of renal replacement therapy, who commenced renal replacement therapy in Australia between 28 June 2006 and 31 December 2016.

Main outcome measures: Time to wait-listing; time to kidney transplantation after wait-listing.

Results: 10 839 patients met the inclusion criteria, of whom 2039 (19%) were Indigenous Australians; 217 Indigenous and 3829 non-Indigenous patients were active on the waiting list at least once during the study period. The hazard ratio (HR) for wait-listing (Indigenous *v* non-Indigenous patients, adjusted for patient- and disease-related factors) in the first year of renal replacement therapy varied with age and remoteness (range, 0.11 [95% CI, 0.07–0.15] to 0.36 [95% CI, 0.16–0.56]); in subsequent years the adjusted HR was 0.90 (95% CI, 0.50–1.6). The adjusted HR for transplantation during the first year of wait-listing did not differ significantly from 1.0; for subsequent years of wait-listing, however, the adjusted HR was 0.40 (95% CI, 0.29–0.55).

Conclusion: Disparities between Indigenous and non-Indigenous patients with end-stage kidney disease in access to kidney transplantation are not explained by patient- or disease-related factors. Changes in policy and practice are needed to reduce these differences.

The incidence and prevalence of end-stage kidney disease are higher among Indigenous than non-Indigenous Australians, particularly among those aged 15–64 years.[1,2] Kidney transplantation is the preferred treatment for most patients with end-stage kidney disease, especially in this age group.[3,4] Disparities between Indigenous and non-Indigenous Australians with regard to wait-listing and transplantation have been identified,[5,6] but the relevant studies are relatively old for an area in which practice has changed substantially. Further, the waiting list information assessed was drawn from the yearly Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) cross-sectional survey of renal units rather than directly from the waiting list and lacked important details, including the date of being placed on the waiting list.[5]

Since 2006, information about kidney transplantation waiting lists is directly incorporated into the ANZDATA registry, and the National Organ Matching Systems (NOMS) database provides the exact date of being added to the waiting list. Subsequent changes to waiting list status (eg, active, interim, removal), however, are not consistently coded. The availability of renal health care has changed substantially since the most recent published reports[5,6] (especially in remote Australia), and the number of deceased donors has increased substantially. We therefore examined the likelihood of Indigenous Australians being placed on the waiting list for transplantation of a kidney from a deceased donor, and the likelihood of transplantation and of death while waiting for transplantation.

Methods

Inclusion and exclusion

All patients registered with ANZDATA who started renal replacement therapy (RRT; dialysis or transplantation) in Australia between 28 June 2006 (NOMS database start date) and 31 December 2016 and were 18–60 years old when they commenced RRT were included. The ANZDATA registry collects data for all patients with end-stage kidney disease treated long term with RRT in Australia. The registry also receives the data from NOMS for all registered patients with end-stage kidney disease on the kidney transplantation waiting list. We analysed a de-identified extract from these data. The patients were classified according to their Indigenous status (Indigenous [Aboriginal and Torres Strait Islander] or non-Indigenous Australians) as reported by the treating hospital and recorded in ANZDATA.

Patients who underwent pre-emptive kidney transplantation or multiple organ transplantation were excluded.

Outcomes

The primary outcomes were:

- Time to wait-listing: time between starting RRT and when the patient was first active on the waiting list. Analyses were censored for factors that lead to patients being removed

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doi: 10.5694/mja18.00304

from the waiting list for transplantation from a deceased donor (transplantation from living donors, recovery of renal function, loss to follow-up, death before activation on the waiting list) and at the end of follow-up (31 December 2016).

- Time to kidney transplantation after wait-listing: the time from first date of active wait-listing to the date of transplantation, censored for living donor transplantation, death, and end of follow-up (31 December 2016). The analysis was not adjusted for intermittent removal of the patient from the waiting list ("de-activation") because this information was not always available.

We examined the association between predictors for wait-listing and the likelihood of placement on the waiting list, including Indigenous status, age at the start of RRT, sex, body mass index (BMI), primary renal disease, comorbid conditions (diabetes, coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease), late referral, year of RRT initiation, remoteness, and the state where RRT started. Types 1 and 2 diabetes were combined because of low patient numbers. The likelihood of transplantation and of death for those on the waiting list was compared by Indigenous status.

Statistical analysis

Frequencies are presented as medians with interquartile ranges (IQRs). Baseline characteristics were compared in Wilcoxon signed rank tests and Pearson χ^2 tests. The frequencies of comorbid conditions in the two groups were compared using logistic regression. Time to wait-listing and time from wait-listing to kidney transplantation were assessed in Cox proportional hazards models, adopting a piecewise approach to maintain the proportional hazards assumption.[7] The models were adjusted for age, sex, BMI, comorbid conditions, primary renal disease, period of RRT commencement (2006–2009, 2010–2013, 2014–2016), late referral, state where RRT was started, and remoteness. Remoteness was defined by Australian Bureau of Statistics (ABS) remoteness categories, by linking ABS postcode of residence concordance data[8] with the postcode recorded in the ANZDATA record for the start of RRT. To account for variation in clinical practice that might affect wait-listing and subsequent transplantation, a shared frailty model[9] was used for the state in which RRT started. Shared frailty is a random component designed to account for variability caused by unobserved individual-level factors unaccounted for by the other predictors in the model. Clinically significant interactions between Indigenous status and other variables (age, sex, BMI, smoking, coronary artery disease, chronic lung disease, cerebrovascular disease, peripheral vascular disease, late referral, primary renal disease, remoteness) were examined; they were included in the final multivariate model if statistically significant. $P < 0.05$ was deemed significant for main effects and interactions. Statistical analyses were conducted in Stata 15.0 (StataCorp).

Ethics approval

The study was approved by the human research ethics branch of the Office of Research Ethics, Compliance and Integrity of the University of Adelaide (reference, H2016-096).

Results

Patients waiting to be placed on the waiting list: baseline characteristics

A total of 10 839 patients were eligible for inclusion, of whom 2039 (19%) were Indigenous Australians. The proportions of women and patients with comorbid conditions (type 2 diabetes, coronary artery disease, cerebrovascular disease, chronic lung disease, peripheral vascular disease), and the prevalence of smoking were higher among Indigenous than non-Indigenous Australians. Most non-Indigenous patients (72%) lived in the major cities of Australia, whereas 38% of Indigenous patients lived in regional areas and 46% in remote or very remote areas (Box 1). The distributions of comorbid conditions in the Indigenous group were similar for all remoteness categories, and were similar for Indigenous and non-Indigenous groups in the same remoteness categories (data not shown). The median time to wait-listing was longer for Indigenous than non-Indigenous patients (942 days [IQR, 439–1775 days] *v* 416 days [IQR, 166–1004 days]) (Box 1).

Likelihood of wait-listing after commencement of renal replacement therapy

In the unadjusted model, the cumulative incidence of wait-listing grew more slowly and was less complete for Indigenous patients (Box 2).

As the hazard ratio (HR) for wait-listing varied with time, we adopted a piecewise approach to analyses for the first year of RRT and for subsequent years.[7] In the first year of RRT, interactions between Indigenous status and each of age and remoteness were statistically significant (Box 3). Accordingly, the adjusted HR (Indigenous *v* non-Indigenous patients) during the first year of RRT varied by age and remoteness. For each combination of remoteness and age group, Indigenous patients were substantially less likely to be wait-listed; the HR declined with age, and was lower for patients from remote regions than those from major cities (Box 4).

For subsequent years of RRT, the adjusted HR (Indigenous *v* non-Indigenous patients) for being added to the waiting list was 0.90 (95% CI, 0.50–1.6; ie, no significant difference); there were no statistically significant interactions between Indigenous status and age or remoteness (data not shown).

Other factors associated with reduced likelihood of wait-listing (all years) were being female, BMI greater than 30 kg/m^2, comorbid conditions, smoking, primary renal disease, and late referral (Box 3).

Characteristics of patients on the kidney transplantation waiting list

Of the 217 Indigenous patients placed on the waiting list, 96 (44.2%) were women, as were 1412 of 3829 non-Indigenous wait-listed patients (36.9%; $P = 0.029$). The median age at the start of RRT was 43 years (IQR, 36–51 years) for Indigenous and 48 years (IQR, 39–55 years) for non-Indigenous patients ($P < 0.001$). The prevalence of comorbid conditions was lower among patients placed on the waiting list than among those who were not (Indigenous and non-Indigenous combined) (Box 5).

All comorbid conditions (except cerebrovascular disease: odds ratio [OR], 0.92, 95% CI, 0.40–1.90) were more frequent among Indigenous than non-Indigenous patients on the waiting list: current smoking (OR, 2.40; 95% CI, 1.72–3.35), diabetes mellitus (types 1 and 2: OR, 5.90; 95% CI, 4.36–7.98), coronary artery disease (OR, 2.53; 95% CI, 1.77–3.60), chronic lung disease (OR, 1.74; 95% CI, 1.10–2.76), and peripheral vascular disease (OR, 2.20; 95% CI, 1.46–3.32); 38.7% of Indigenous patients and 64.4% of non-Indigenous patients on the transplant waiting list had no comorbid conditions ($P < 0.001$).

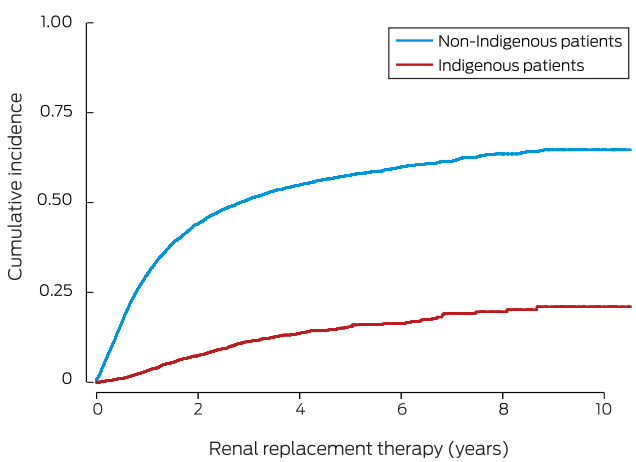
The median time to kidney transplantation after wait-listing was 266 days (IQR, 70–882 days) for Indigenous patients and 378 days

1 Baseline characteristics of the 10 839 eligible patients included in the study

Baseline characteristics	Non-Indigenous Australians	Indigenous Australians	*P*
Number of patients	8800	2039	
Age at renal replacement therapy initiation (years), median (IQR)	50.0 (41.0–56.0)	49.0 (41.0–54.0)	< 0.001
Sex (women)	3298 (37.5%)	1106 (54.2%)	< 0.001
Remoteness category			< 0.001
Major cities	6369 (72.4%)	297 (14.6%)	
Inner regional	1524 (17.3%)	165 (8.1%)	
Outer regional	708 (8.0%)	611 (30.0%)	
Remote	91 (1.0%)	471 (23.1%)	
Very remote	31 (0.4%)	471 (23.1%)	
Missing data	77 (0.9%)	24 (1.2%)	
Body mass index (kg/m^2), median (IQR)	27.4 (23.3–32.9)	28.3 (23.9–33.3)	< 0.001
Current smoker (start of renal replacement therapy)	1456 (16.8%)	637 (31.7%)	< 0.001
Comorbid conditions			
Diabetes	3273 (37.4%)	1624 (79.7%)	< 0.001
Coronary artery disease	1980 (22.6%)	730 (36.0%)	< 0.001
Peripheral vascular disease	1435 (16.4%)	493 (24.3%)	< 0.001
Cerebrovascular disease	754 (8.6%)	212 (10.4%)	0.010
Chronic lung disease	942 (10.8%)	332 (16.4%)	< 0.001
None	4206 (48.2%)	260 (12.8%)	< 0.001
Late referral	1954 (22.2%)	476 (23.3%)	0.06
Primary renal disease			< 0.001
Glomerulonephritis, polycystic, hypertensive, diabetic nephropathy, reflux	7223 (83.0%)	1851 (91.5%)	
Other	1479 (17.0%)	171 (8.5%)	
Outcome			< 0.001
Wait-listed	3829 (43.5%)	217 (10.6%)	
Transplantation before wait-listing	20 (0.2%)	0	
Death before wait-listing	1604 (18.2%)	644 (31.6%)	
Censored	3347 (38.0%)	1178 (57.8%)	
Age at wait-listing (years), median (IQR)	49.0 (39.0–56.0)	46.0 (38.0–53.0)	0.004
Time from RRT start to wait-listing (days), median (IQR)	416.0 (166.5–1004.0)	942.0 (439.0–1775.0)	< 0.001

IQR = interquartile range. ◆

2 Unadjusted Kaplan–Meier curve for cumulative incidence of wait-listing after initiation of renal replacement therapy, by Indigenous status



(IQR, 125–885 days) for non-Indigenous patients ($P < 0.029$). Of 4046 participants on the waiting list, 2552 (63.1%) received a deceased donor kidney: 2417 of non-Indigenous (63.1%) and 135 Indigenous patients (62.2%).

After initial placement on the transplant waiting list, 164 patients died without receiving a deceased donor kidney: 147 non-Indigenous (3.8%) and 17 Indigenous patients (7.8%). The death rate from the date of initial listing to the end of the study period was 48.3 per 1000 person-years (95% CI, 30.1–77.8 per 1000 person-years) for the Indigenous group and 22.9 per 1000 person-years (95% CI, 19.5–27.0 per 1000 person-years) for the non-Indigenous group. Among those active on the transplant waiting list, the adjusted HR (Indigenous *v* non-Indigenous) for death after initial placement on the waiting list was 0.78 (95% CI, 0.43–1.42).

Likelihood of transplantation among those on the transplant waiting list

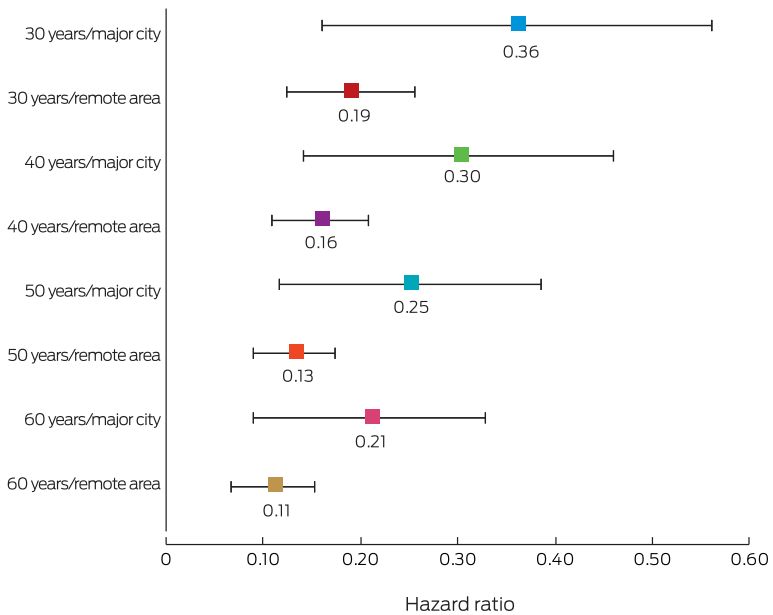
The likelihood of transplantation for Indigenous patients during the first year of wait-listing was similar to that for non-Indigenous

3 Multivariate Cox model of being placed on the waiting list for kidney transplantation, with frailty shared at state level

	Adjusted hazard ratio* (95% CI)	*P*
Indigenous Australian (first year of renal replacement therapy)	0.62 (0.29–1.35)	0.23
Indigenous Australian (subsequent years of renal replacement therapy)	0.90 (0.50–1.62)	0.73
Other covariates		
Very remote/remote/regional areas (*v* major cities)	0.92 (0.85–0.99)	0.019
Interaction: Indigenous status and remote location	0.53 (0.29–0.97)	0.038
Age (per year)	0.99 (0.987–0.993)	< 0.001
Interaction: Indigenous status and age	0.98 (0.97–0.99)	0.006
Sex (men *v* women)	1.18 (1.10–1.26)	< 0.001
Body mass index ≥ 30 kg/m^2	0.61 (0.57–0.66)	< 0.001
Primary renal disease†	0.58 (0.53–0.64)	< 0.001
Diabetes	0.41 (0.38–0.45)	< 0.001
Coronary artery disease	0.66 (0.60–0.73)	< 0.001
Chronic lung disease	0.68 (0.60–0.78)	< 0.001
Peripheral vascular disease	0.72 (0.64–0.82)	< 0.001
Cerebrovascular disease	0.60 (0.51–0.70)	< 0.001
Smoker	0.47 (0.43–0.52)	< 0.001
Late referral	0.68 (0.62–0.73)	< 0.001
Renal replacement therapy, 2010–2013 (*v* 2006–2009)	1.07 (1.00–1.16)	0.039
Renal replacement therapy, 2014–2016 (*v* 2006–2009)	1.04 (0.95–1.13)	0.40

* Adjusted for age at the start of renal replacement therapy, sex, body mass index, smoking, diabetes, peripheral vascular disease, coronary artery disease, cerebrovascular disease, late referral and state where renal replacement therapy was started). † Including category 1: glomerulonephritis, polycystic kidney disease, reflux nephropathy, hypertensive nephropathy, diabetic nephropathy; category 2: other diseases reported as causing primary renal disease. ◆

4 Adjusted hazard ratios* (with 95% confidence intervals) for wait-listing during the first year of renal replacement therapy (Indigenous *v* non-Indigenous patients), by age and remoteness category



* Adjusted for age at the start of renal replacement therapy, sex, body mass index, smoking, diabetes, peripheral vascular disease, coronary artery disease, cerebrovascular disease, late referral and state where renal replacement therapy was started). Remote area refers to inner regional, outer regional, remote and very remote areas combined. ◆

patients, and did not vary over time. For transplantation in patients aged 40 in the first year of wait-listing, the adjusted HR (Indigenous *v* non-Indigenous) for the RRT period 2006–2009 was 1.4 (95% CI, 0.9–1.9), for 2010–2013 it was 1.8 (95% CI, 1.2–2.4), and for 2014–2016 it was 1.6 (95% CI, 0.6–2.6). There was no statistically significant interaction between Indigenous status with period of RRT during the first year of treatment.

The adjusted HR for transplantation (Indigenous *v* non-Indigenous, all periods of RRT) for subsequent years of wait-listing was 0.4 (95% CI, 0.3–0.6). Other factors that significantly influenced the probability of kidney transplantation were age (per year: HR, 1.01; 95% CI, 1.00–1.01), sex (men *v* women: HR, 1.18; 95% CI, 1.09–1.28), BMI (≥ 30 kg/m^2 *v* < 30 kg/m^2: HR, 1.15; 95% CI, 1.05–1.25), and diabetes (HR, 0.85; 95% CI, 0.76–0.94) (Box 6).

Discussion

Despite the increasing availability of nephrology services in recent years and national criteria for assessing patients to be placed on the kidney transplantation waiting list,[10,11] Indigenous Australians undergoing dialysis are still substantially less likely than non-Indigenous Australians to be placed on the waiting list. Multivariate analysis indicated that this disparity was not explained by differences in kidney disease aetiology,

5 Comorbid conditions in patients with end-stage kidney stage placed or not placed on the waiting list for kidney transplantation

Comorbid condition	Odds ratio* (95% CI)
Current smoker	0.49 (0.45–0.54)
Diabetes (types 1 and 2)	0.32 (0.29–0.35)
Coronary artery disease	0.44 (0.41–0.48)
Cerebrovascular disease	0.41 (0.36–0.48)
Peripheral vascular disease	0.37 (0.33–0.41)
Chronic lung disease	0.48 (0.42–0.54)

CI = confidence interval. * Patients who were wait-listed *v* patients who were not wait-listed during the follow-up period, adjusted for age at the start of renal replacement therapy, sex, and Indigenous status. ◆

BMI, comorbid conditions, late referral for RRT, location of treatment, or remoteness, and has not changed with time. The difference was greater among patients who are older and living in remote areas. For people on the waiting list, the likelihood of receiving a transplant is higher in the first year and is similar for Indigenous and non-Indigenous Australians (43.8% *v* 31.9% underwent transplantation in the first year of wait-listing), but is significantly lower for Indigenous patients in subsequent years.

We analysed more accurate and detailed information on the waiting list status of patients than earlier studies, including exact dates of listing[5] and more recent data (2006–2016). Our findings therefore reflect current clinical practice, with nephrology services well established in more remote areas of central and northern Australia. It is notable, however, that the unexplained differences we found are similar to those reported 20 years ago.[6]

The difference in likelihood of wait-listing was significant for the first year of RRT and for patients in remote locations, but not during subsequent years of RRT. This is likely to reflect geographic factors (living further from major centres is a barrier to testing and clinical review as part of transplantation assessment)[12] and factors associated with remoteness not assessed in our study, such as cultural differences, communication problems, and different understanding of health.[5,13,14] In addition, patients in remote areas may spend much of their first year on dialysis dealing with problems of re-location and adjusting to the demands of treatment rather than assessment for transplantation. The reduction of these differences over time suggests that this situation can be improved.

The difference between Indigenous and non-Indigenous patients in the likelihood of being placed on the transplantation waiting list has not changed with time. Placement on the transplant waiting list is the culmination of a series of steps and assessments, including the patient deciding to pursue this path and the treating clinician registering this decision, initial medical assessment and referral for consideration for transplantation, education of the patient about the merits of transplantation, and assessment by the transplantation unit. We do not know how many patients in our study were not referred for wait-listing because they decided not to proceed. However, in a recent analysis of comprehensive interviews of 143 Indigenous patients with end-stage kidney disease

6 Multivariate Cox model of the likelihood of receiving a deceased donor kidney after being placed on the waiting list for transplantation, with frailty shared at state level

	Adjusted hazard ratio* (95% CI)	*P*
Indigenous Australian: first year on waiting list	1.24 (0.89–1.73)	0.20
Indigenous Australian: subsequent years on waiting list	0.40 (0.29–0.55)	< 0.001
Other covariates		
Sex (men *v* women)	1.18 (1.09–1.28)	< 0.001
Age (per year)	1.01 (1.00–1.01)	0.007
Body mass index ≥ 30 kg/m^2	1.15 (1.05–1.25)	0.002
Primary renal disease†	1.02 (0.91–1.14)	0.76
Diabetes	0.85 (0.76–0.94)	0.002
Chronic lung disease	0.97 (0.82–1.14)	0.68
Cerebrovascular disease	1.20 (0.99–1.46)	0.07
Coronary artery disease	0.91 (0.80–1.03)	0.14
Peripheral vascular disease	0.99 (0.84–1.16)	0.90
Smoker	1.04 (0.92–1.17)	0.58
Late referral	1.09 (0.99–1.21)	0.09
Very remote/remote/regional areas (*v* major cities)	0.99 (0.91–1.09)	0.89
Renal replacement therapy, 2010–2013 (*v* 2006–2009)	1.49 (1.36–1.62)	< 0.001
Renal replacement therapy, 2014–2016 (*v* 2006–2009)	1.46 (1.27–1.67)	< 0.001
Interaction: Indigenous status and period of renal replacement therapy		
Indigenous Australian: renal replacement therapy, 2010–2013	0.88 (0.56–1.36)	0.56
Indigenous Australian: renal replacement therapy, 2014–2016	0.80 (0.40–1.58)	0.52

* Adjusted for age at the start of renal replacement therapy, sex, body mass index, smoking, diabetes, peripheral vascular disease, coronary artery disease, cerebrovascular disease, late referral and state where renal replacement therapy was started). † Including category 1: glomerulonephritis, polycystic kidney disease, reflux nephropathy, hypertensive nephropathy, diabetic nephropathy; category 2: other diseases reported as causing primary renal disease. ◆

from 26 urban, rural, and remote sites across Australia, 90% of participants expressed strong interest in receiving a transplant.[15]

In the jurisdictions in Australia where most transplantations for Indigenous patients are performed (South Australia, Northern Territory, Western Australia), about 80% of kidneys are allocated according to waiting time,[10] calculated from the start of RRT for wait-listed patients. Delays in being accepted for the waiting list consequently lead to patients being near the top of the list at the time of listing, increasing their likelihood of transplantation soon after listing. This is reflected in the shorter median time to transplantation after wait-listing and higher rates of transplantation in the first year after placement on the waiting list, after which the transplantation rate falls.

Strategies for improving access to and use of renal services by Indigenous patients have been implemented in recent decades.[16] Much more is known about challenges to providing high quality renal care for Indigenous patients,[5,14] but there have been no specific national policy changes with the aim of improving access to transplantation. At the clinical level, outcomes after transplantation, in terms of both graft function and patient survival, are considerably poorer for Indigenous patients,[17] particularly for those from remote areas.[18] The potential benefits for patients must be balanced against these risks when making decisions about treatment.

Limitations

The relatively small number of transplants received by Indigenous patients during 2006–2016, the limited data on comorbid conditions, and the difficulty of analysing the complex interactions involved in the effect of remoteness on access to transplantation all complicate interpretation of our findings. There are probably a number of other, unmeasured factors that influence wait-listing and transplantation rates.[19] In particular, the ANZDATA registry does not record active infections or the severity of comorbid conditions, which may have led to our underestimating the effect of comorbid conditions on wait-listing and access to transplantation. Further relevant socio-demographic factors — including first language spoken, education level, health literacy, housing status — could also affect access to transplantation. Area-level socio-economic indices for the Indigenous residents of a postcode, rather than all residents, are not readily available. Further, registry data do not account for the re-location of many Indigenous Australians to receive dialysis treatment; that is, their postcode at the start of RRT may not reflect their community of origin. All these factors could delay wait-listing.[13,14]

Conclusion

Indigenous patients with end-stage kidney disease are less likely than non-Indigenous Australians to be wait-listed for transplantation. This disparity was particularly marked for the first year of RRT, and was not explained by the patient- and disease-related factors assessed. The difference in access early in RRT may reflect remoteness of Indigenous patients undergoing dialysis, and this should be a priority area for improving health service delivery. As the burden of comorbid conditions among Indigenous patients on the transplantation waiting list was higher than for non-Indigenous patients, maintaining health and preventing the development of comorbid conditions should receive more attention. Further work at policy and practice levels is required to improve successful kidney transplantation for Indigenous Australians.

Competing interests: No relevant disclosures.

Received 24 Mar 2018, accepted 4 July 2018. ■

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We identified that Indigenous patients were less likely than non-Indigenous patients to be added to the transplantation waiting list during the first year of kidney replacement therapy; this disparity was not completely explained by differences in patient- and disease-related factors. Given, the significant effect of comorbid conditions among Indigenous patients on the transplantation waiting list, preventing the development of comorbidities should also be prioritised. The likelihood of transplantation during the first year after placement on the transplant waiting list was similar for both groups but significantly lower for Indigenous patients in subsequent years. The implications of these findings highlight that changes in policy and practice are needed to improve the access of Indigenous patients to kidney transplantation. (77) Whether institutional racism could be among the unmeasured confounders, needs careful consideration. Our findings were successful in contributing to the development of National indigenous Kidney Transplant Taskforce (NIKTT). (85)

CHAPTER 3

Association between facility haemodialysis attendance and the chance of placement on the transplant waiting list, and transplant outcomes

From chapter 2, we learnt that the chance of placement on the transplant waiting list for kidney transplant is lower among Indigenous Australians. Little is known about the association of dialysis attendance with placement on the transplant waiting list or transplant outcomes. Previous studies indicate that when dialysis attendance is less than prescribed, nephrologists' decisions to refer the patient for transplantation may be affected. (83) Therefore this study was conducted to examine the third aim of the thesis, which is described in this chapter. The specific aim of this chapter is:

1. To examine relationships between Indigenous patients' facility haemodialysis attendance and the chance of placement on the transplant waiting list, transplantation and transplant outcomes.

Synopsis:

The relationship of facility haemodialysis (FHD) attendance in the first two years of kidney replacement therapy (KRT) initiation with subsequent placement on the transplant waiting list, and kidney transplant outcome in the NT based Indigenous Australians with ESKD was examined.

Methods: Existing hospital separation dataset was linked with waiting list information from the ANZDATA registry. The study examines patients who started KRT from 1st January 1995 to 31 December 2011. Because, the quality of available data changed from 28 June 2006, outcome measures and analysis for the two periods have been differentiated. Three principal outcomes were examined. The first was transplantation (as an indirect measure for placement on the transplant waiting list) for all participants. An additional outcome for those who started FHD from 28th June 2006 until 31st December 2011 and were wait-listed by 30th June 2012, was first active placement on the deceased donor waiting list. Finally, all-cause graft loss post-transplantation, including patient death was the outcome measure for patients who started KRT for the whole period covering 1st January 1995 to 31st December 2011 and were transplanted by 30th June 2012. Dialysis attendance in the first two years from KRT start was the exposure variable.

Results: The study included 670 people receiving FHD, of whom 301 (44.9%) of 670 on FHD had attendance ≤2.5 sessions/week. Of these, 44 received a deceased donor kidney transplant, of whom 38 (86.4%) sustained graft loss. Additionally, of those who commenced KRT from 28th June 2006, 5 were wait-listed. Compared to those with attendance >2.5 dialysis sessions/week during the study period, participants with ≤2.5 dialysis sessions/week had the adjusted hazard ratios (HR) of

0.1 (95% confidence interval (CI), 0.03- 0.24) for a receipt of a kidney transplant and 0.4 (95% CI, 0.1-2.2) for graft loss.

Conclusions: The chance of kidney transplant and placement on the waiting list were extremely low, and this limited the statistical power of the study. Nonetheless, FHD attendance ≤2.5 dialysis sessions/week was associated with a reduced likelihood of transplantation. Strategies to increase placement on the transplant waiting list and kidney transplantation should be prioritised.

Introduction:

In Chapter 2, it was shown that the likelihood of placement on the transplant waiting list and kidney transplantation among Indigenous Australians is substantially lower compared with their non-indigenous counterparts, especially among those living in remote areas. (77) A range of patient-, provider-, and health system factors have been postulated to underpin disparities in waitlist access. A critical factor in the process of transplantation is the initiation of workup and referral by the responsible nephrologist. While dialysis attendance is not an explicit part of the pre-transplant assessment process, it is likely to form part of the implicit assessment thereby affecting nephrologists' decision to refer the patient for transplant work-up and wait-listing. Because, specific guidelines to identify patients at high risk of non-adherence post-transplantation do not exist, dialysis attendance is often used as a marker of compliance to the medical treatment. (86) A national survey conducted in Australia suggested that when patients attend fewer than the prescribed number of dialysis sessions, it may affect nephrologists' decision to refer patients for kidney transplantation due to concerns about outcomes in the post-transplant period. (83)

Typically, haemodialysis is prescribed three times a week for patients with end-stage kidney disease (ESKD). Attending fewer than the prescribed number of dialysis sessions is associated with increased mortality. In studies conducted among United States dialysis patients, the mortality rate increased by 20-25% and hospitalisation by 16% in those who missed dialysis once per month. (87, 88) There is a paucity of data on the effect of dialysis attendance among Australian ESKD patients, including Indigenous Australians. Previous studies have described decreased attendance at facility haemodialysis (FHD) among the Northern Territory (NT) based ESKD patients. (89) However, little is known about the association between dialysis

attendance and placement on the transplant waiting list, access to and outcomes of subsequent kidney transplantation. (90) Therefore, this study was conducted to examine:

1. The relationship between dialysis attendance, placement on the transplant waiting list and transplantation in NT based Indigenous Australians with ESKD.
2. The relationship of dialysis attendance with subsequent kidney transplantation outcomes in NT based Indigenous transplant recipients.

Methods

Hospital separations data for NT based Indigenous Australians with ESKD for the period 1st January 1995 to 30th June 2011 was used. These data were linked to demographic, comorbidity and transplant-related information from the ANZDATA Registry. As mentioned in chapter two, the registry collects data of patients with ESKD treated with dialysis and transplantation in Australia and New Zealand. The registry also receives waiting list information from the National Organ Matching System (NOMS) database. Data linkage of hospital separation data and the ANZDATA Registry information was performed for a previous project by the NT Government Department of Health's Health Gains Planning Branch. (89) A de-identified extract was used for analysis in our study.

All patients on haemodialysis at 90 days after kidney replacement therapy (KRT) start and wait-listed or received a kidney transplant by 30th June 2012 were included.

Exposure: The primary exposure variable for all outcomes was outpatient dialysis attendance at FHD during the study period, and in the first two years from KRT initiation.

Outcome: Deceased donor transplantation (which necessarily requires a placement on the transplant waiting list and therefore is an indirect measure for the same) was the outcome measure for participants who were on FHD.

For those who were transplanted, graft loss (loss of graft function requiring dialysis or patient death) was examined.

Subgroup analysis: For participants who started dialysis from 28th June 2006 (NOMS start date) to 31st December 2011, precise information on the date of

placement on the transplant waiting list was available. Therefore, additional analysis was conducted for this group to examine the chance of first active placement on the waiting list.

These dates were determined by the availability of comprehensive data about the timing of placement on the transplant waiting list. However, it is also important to note that the study is part of a PhD thesis which was started in January 2016. The dataset used for the study with attendance information until 2011 was, therefore, appropriate when the project was started. This allowed follow-up of the participants for a minimum period of six months.

Statistical analysis

Wilcoxon's signed-rank test and Pearson's $\chi 2$ were used for comparison of baseline characteristics. Frequency measures were presented as the mean (standard deviation, SD) or median (interquartile range [IQR]). Comorbidities between the groups were compared using logistic regression. Cox proportional hazards model was used to estimate the likelihood of placement on the transplant waiting list, transplantation, and outcomes of kidney transplant. Adjusted statistical models included age, gender (male), comorbidities at the initiation of kidney replacement therapy, and year of initiation of KRT unless mentioned otherwise. Clinically significant interactions between ethnicity and other variables were tested separately in the univariate model. These interactions were included in the final multivariate model if statistically significant. P-values <0.05 were considered statistically significant. Stata version 15 (College Station, TX) was used for statistical analysis.

Sensitivity analysis was performed to examine the association of various categories of dialysis attendance with kidney transplantation, the chance of

placement on the transplant waiting list, and transplant outcomes. These categories of dialysis attendance which were examined and compared were:

1. Dialysis attendance of <2 sessions, 2 to 2.5 sessions and ≥2.5 sessions/week
2. Dialysis attendance of <2.5 sessions/ week vs. >2.5 sessions/week
3. Dialysis attendance of <2.75 sessions/ weeks vs. >2.75 session/week
4. Comparison of the lowest quartile with the highest quartile of dialysis attendance
5. Comparison of the lowest quintile with the highest quintile of dialysis attendance

No difference in the final outputs for the chance of transplantation, placement on transplant waiting list or transplant outcome was seen between the attendance categories listed above. To optimise statistical power, the final analysis compared to ≤2.5 and > 2.5 sessions per week (missing fewer than two dialysis sessions a month) of dialysis attendance. Results comparing quintiles are also presented in this chapter.

Additional sensitivity analysis examined different periods during which the dialysis attendance could be measured to derive a clinically meaningful interpretation. The categories of study period during which dialysis attendance was measured were:

1. Total dialysis attendance within the study period for included participants. E.g. Participant 'A' started KRT on 1st Jan 1995 and was waitlisted on 30th June 2012. Weekly dialysis attendance in the entire period from 1st January 1995 to 30th June 2012 was used for analysis.

2. Dialysis attendance in the first two years following KRT start. E.g. In the example of Participant "A"- weekly dialysis attendance in the period of 1st Jan 1995 to 31st Dec 1997 was used.
3. Dialysis attendance two years before the placement on transplant waiting list or transplantation. In the same example of participant "A", weekly dialysis attendance in the period of 1st July 2010 to 30th June 2012 was used.
4. For those participants with none of these outcomes, weekly dialysis attendance in the period two year before death or 30th June 2012 was used.

Cox regression analysis using these covariates did not result in a difference in the overall interpretation of the findings in terms of the association of dialysis attendance and the chance of placement on the transplant waiting list or transplant outcome. Among participants who were not wait-listed or transplanted, the comorbidity burden continued to increase with time spent on dialysis. Therefore on clinical grounds and the nature of data available, the final analysis used the dialysis attendance in the first two years since the initiation of KRT.

The following formula was used to calculate FHD attendance frequency:

$$\left\{ \frac{\text{Total number of outpatient dialysis sessions}}{\text{Total period during which FHD was performed in the NT in days}} \right\} \text{X } 7$$

Calculation of dialysis attendance did not include time spent in hospital overnight, interstate, or time receiving peritoneal or home haemodialysis.

Ethical considerations:

This study was approved by the University of Adelaide Human Research Ethics Committee, and the NT Department of Health and Menzies School of Health Research Human Research Ethics Committee, Charles Darwin

University. Human Research Ethics approval for Aboriginal and Torres Strait Islanders was incorporated into the Menzies and the University of Adelaide Human Research Ethics Committee.

Results:

There were 890 Indigenous participants who started KRT from 1st January 1995 to 30th June 2011. Of these, 670 received FHD in the first two years following KRT initiation. Forty-four of 670 participants received a deceased donor transplant by 30th June 2012. Two hundred sixty-seven participants started KRT from 28th June 2006 to 31st December 2011. Figure 3.1 shows the distribution of included participants.

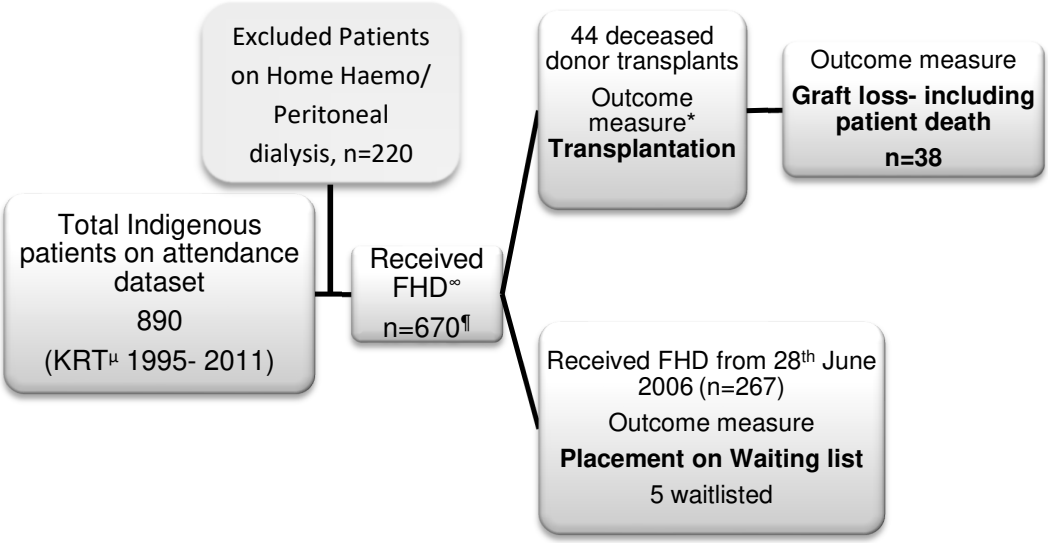


Figure 3.1: Flowchart showing the distribution of included patients *Outcome measured for this group was the receipt of a deceased donor transplant by 30th June 2012 (which necessarily requires a placement on the transplant waiting list)

¶Total number of patients who started KRT from 1st January 1995 to 31st December 2011, who were exclusively on facility haemodialysis 90 days of KRT start ∞ FHD Facility haemodialysis μKRT Kidney replacement therapy

Baseline characteristics (Table 3.1& 3.2):

The baseline characteristics, according to dialysis attendance, are shown in Table 3.1. Dialysis attendance was ≤2.5 sessions/ week in 301 (44.9%) participants. Six of 44 transplanted participants (13.6%) had attendance ≤2.5 sessions/ week.

All participants	Overall Dialysis attendance		P-value
	≤2.5 sessions/week	>2.5 sessions/week	
Number of participants in each category	301	369	
Transplanted or Wait-listed	6 (2)	38 (10.3)	<0.01
Age at KRT¶ start, median (IQR)	46.0 (38, 54)	52 (45, 59)	<0.01
Gender (Male)	136 (45.2%)	139 (37.7%)	0.1
Late Referral	93 (31.4%)	100 (27.3%)	0.3
Current Smoker	94 (31.2%)	85 (23.0%)	<0.05
Diabetes (present or absent)	224 (74.4%)	298 (80.8%)	<0.05
Coronary artery disease	78 (25.9%)	131 (35.5%)	<0.01
Chronic lung disease	45 (15.0%)	67 (18.2%)	0.3
Cerebrovascular disease	17 (5.6%)	49 (13.3%)	<0.01
Peripheral vascular disease	53 (17.6%)	104 (28.2%)	<0.01

Table 3.1: Baseline characteristics of all study participants (n=670) according to their overall dialysis attendance * IQR- Inter-quartile range ¶KRT- Kidney replacement therapy

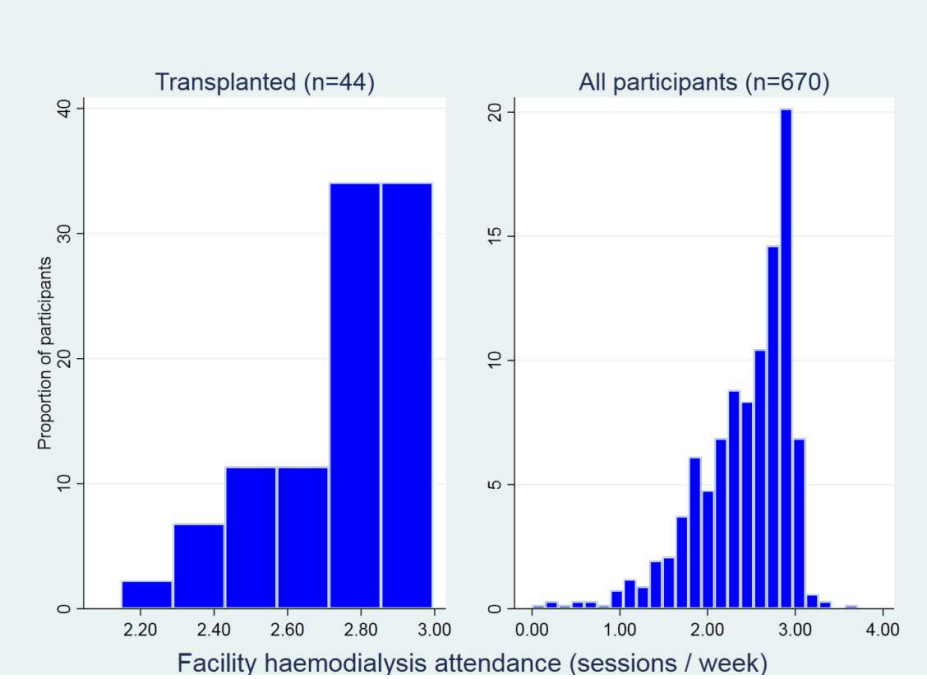
Comparison of the baseline characteristics of participants with dialysis attendance ≤2.5 sessions/week and >2.5 sessions/week and received kidney transplantation is shown in Table 3.2.

Transplanted	FHD ≤2.5 sessions/ week	FHD >2.5 sessions/ week	P-value
N=44	6	38	
Age at KRT¶ start, median (IQR*)	36.5 (31, 44)	45.5 (41, 50)	0.1
Age at Transplant, median (IQR)	40 (34, 48)	49 (44, 54)	0.1
Gender (Male)	5 (83%)	22 (58%)	0.2
Late Referral	5 (83%)	14 (37%)	<0.05
Current Smoker	5 (83%)	12 (32%)	<0.05
Diabetes (present or absent)	2 (33%)	22 (58%)	0.3
Coronary artery disease	0 (0%)	5 (13%)	0.4
Chronic lung disease	1 (17%)	1 (3%)	0.1
Cerebrovascular disease	0 (0%)	4 (11%)	0.4
Peripheral vascular disease	1 (17%)	5 (13%)	0.8

Table 3.2: Baseline characteristics of the transplanted participants

* IQR- Inter-quartile range ¶ KRT- kidney replacement therapy

The distribution of the weekly haemodialysis frequency in the first two years of KRT, among for those who received kidney transplantation, and all participants is shown in Figure 3.2.



A **B**

Figure 3.2: A. Weekly attendance at Facility Haemodialysis for participants who were transplanted B. Weekly attendance at Facility Haemodialysis for all study participants

Haemodialysis attendance and the likelihood of transplantation:

Of 670 participants treated with FHD, 44 participants (6.6%) received a deceased donor kidney transplant by 30th June 2012. Complete information on dialysis attendance was available for 654 participants. The median time to transplant from KRT initiation was 3.1 years (Interquartile range (IQR), 2.8-3.5) among those with attendance ≤2.5 sessions/week and 2.9 years (IQR, 2.3-4.0) for participants with attendance >2.5 sessions/week, p-value 0.8. The majority of participants with dialysis attendance ≤2.5 sessions/week (n=268 out of 301, 89%) were in the lower two quintiles of dialysis attendance.

a. Dialysis attendance in the first two years from the KRT start and chance of transplantation:

The unadjusted hazard ratio (HR) for transplantation among participants with ≤2.5 sessions/week dialysis attendance in the first two years from the KRT start was 0.4 (95% CI, 0.2-0.8) when compared to participants with dialysis attendance >2.5 sessions/week. The adjusted HR for transplantation was 0.2 (95% CI, 0.1-0.5) in participants with dialysis attendance ≤2.5 sessions/ week in the first two years from the KRT.

No participants with dialysis attendance in the lowest quintile in the first two years of dialysis attendance received a kidney transplant during the study period. Compared to participants with dialysis attendance in the highest quintile in the first two years, the unadjusted HR for transplantation for participants with attendance in the 2nd lowest quintile was 4.1 (95% CI, 0.8-22.4) and the adjusted HR was 2.4 (95% CI, 0.4-13.2).

b. Overall dialysis attendance during the study period and chance of transplantation:

The unadjusted HR for transplantation among participants with ≤2.5 sessions/week overall dialysis attendance in the study period was 0.3 (95% CI, 0.1- 0.6) and the adjusted HR was 0.1 (95% CI, 0.03- 0.24).

Finally, compared to participants with the overall dialysis attendance in the highest quintile, the unadjusted HR for transplantation for participants with attendance in the 2nd lowest quintile was 0.4 (95% CI, 0.1-1.3), and the adjusted HR was 0.2 (95% CI, 0.1-0.6).

Haemodialysis attendance and outcome (graft loss or patient death) among participants on FHD:

Thirty-eight of the 44 FHD participants who received kidney transplants, experienced graft loss. The overall median graft survival for participants with dialysis attendance ≤2.5 and >2.5 sessions/ week was 2.9 years.

a. Dialysis attendance in the first two years from the KRT start and chance of graft loss:

Compared to the participants with dialysis attendance >2.5 sessions/week in the first two years of KRT, the unadjusted HR for graft loss for participants with dialysis attendance ≤2.5 sessions/ week was 0.9 (95% CI, 0.4-2.4) and the adjusted HR was 0.3 (95% CI, 0.1-1.6). Compared to participants with dialysis attendance in the highest quintile in the first two years of KRT start, unadjusted HR for graft loss for participants with dialysis attendance in the second lowest quintile was 5.7 (95% CI, 0.6- 57.8), and the adjusted HR was 9.8 (95% CI, 0.7-140.7). Participants with dialysis attendance in the lowest quintile did not receive a kidney transplant.

b. Overall dialysis attendance during the study period and chance of graft loss:

The unadjusted HR for graft loss for participants with overall dialysis attendance ≤2.5 sessions/ week in the study period was 1.1 (95% CI, 0.4-2.9) and the adjusted HR was 0.4 (95% CI, 0.1-2.2). The unadjusted HR for graft loss for participants with dialysis attendance in the second lowest quintile in the overall study period was 1.6 (95% CI, 0.4-6.2) when compared to participants with attendance in the highest quintile, and the adjusted HR was 1.7 (95% CI, 0.4- 6.9).

Haemodialysis attendance and the likelihood of placement on the transplant waiting list among participants who started KRT from 28th June 2006 to 31st December 2011:

Among the participants who started KRT from 28th June 2006 to 31st December 2011, there were 267 participants on FHD at 90 days from KRT start. Information on FHD attendance in the first two years from the KRT start was available for 256 participants, while 253 participants had complete information on dialysis attendance for the overall study period. Of the 256, only 5 participants (1.9%) were waitlisted by 30th June 2012. Among these, 3 participants received deceased donor transplants. One hundred and fifty-six (60.9%) participants had dialysis attendance ≤2.5 sessions/ week in the first two years from KRT start. Median (IQR) time to placement on the transplant waiting list was 2.8 years (1.6-3.4) among participants with dialysis attendance ≤2.5 sessions/ week, and 3.7 years (3.6-3.9) for those with attendance >2.5 sessions/ week. Due to the small number of participants achieving the outcome measured, statistical power for further analysis was

limited. Table 3.3 shows time to placement on the transplant waiting list for the 5 participants.

Participant	Time to Placement on the transplant waiting list (in years)
1	1.6
2	2.8
3	3.4
4	3.5
5	3.9

Table 3.3: Time to Placement on the transplant waiting list (in years) for participants waitlisted by 30th June 2012

Table 3.4 shows the hazard ratio for transplantation, graft loss and chance of placement on the transplant waiting list according to the dialysis attendance.

Adjusted Hazard Ratio (95% Confidence Interval)				
	Dialysis attendance in the first two years from KRT* ≤2.5 sessions/ week	Overall dialysis attendance ≤2.5 sessions/ week	Dialysis attendance in second lowest quintile# compared to the highest quintile in the first two years from KRT* start	Overall dialysis attendance in second lowest quintile# compared to the highest quintile
Transplantation	0.2 (95% CI, 0.07-0.49)	0.1 (95% CI, 0.03- 0.24)	2.4 (95% CI, 0.42-13.23)	0.2 (95% CI, 0.05-0.59)
Graft loss	0.3 (95% CI, 0.06-1.62)	0.4 (95% CI, 0.09-2.15)	9.8 (95% CI, 0.68-140.65)	1.7 (95% CI, 0.41- 6.89)
Placement on the transplant waiting list: Total of 5 participants placed on the waiting list, statistical power limited for cox regression				

Table 3.4: Hazard ratio (HR) for transplantation, Graft loss and chance of placement on the transplant waiting list. *KRT kidney replacement therapy #participants with dialysis attendance in the first quintile did not receive kidney transplantation

HR is shown according to participants' dialysis attendance in the first two years from KRT start, attendance throughout the study period (compared to dialysis attendance >2.5 sessions/ week) and participants with dialysis attendance in the second lowest quintile (compared to highest (5^{th}) quintile) in the first two years from KRT start. Multivariate cox regression adjusted for: gender, age, comorbidities, smoking status at KRT start, and year of KRT start

Discussion:

The most striking finding of this study is the extremely low proportion of participants on the transplant waiting list. Nonetheless, the likelihood of kidney transplantation was lower among participants with attendance ≤2.5 sessions/ week, and those with dialysis attendance in the lowest quintile did not receive kidney transplantation.

In regards to aim 2 of this study, no association was found between kidney transplant outcome (graft loss and patient death) and dialysis attendance. The statistical power of the analysis was limited by a low number of transplantation among the study participants.

To our knowledge, this is the first study evaluating the relationship between dialysis attendance with a chance of placement on the transplant waiting list and kidney transplant outcomes in Indigenous Australians with ESKD. Furthermore, there is a paucity of data examining treatment adherence using parameters other than dialysis attendance among Indigenous Australians with ESKD.

Although the health systems are very different, our findings are similar to the observations made by Hucker et al. and Denhaerynck et al. (90, 91) Both of these studies originated outside of Australia, and neither included Indigenous patients of their regions. Hucker et al. (90) studied the pre-transplantation adherence behaviours in their dialysis patients and did not find a direct relationship with post-transplantation adherence to treatment. Denhaerynck et al. (91) suggested that the determinants of non-adherence in the post-transplant period were not related to dialysis attendance.

A substantial number of participants on FHD in our study had ≤2.5 sessions/ week of dialysis attendance, i.e. missing at least two sessions of dialysis per month. It is not known how this compares to the rest of Australia or Indigenous Australians from other parts of Australia. Findings similar to our study were reported by Gray et al. (92) & Chenitz et al. from the US. (93) Gray et al. reported that haemodialysis patients missed 9.9% of all treatments in their study, which comprised 40% of United States dialysis population. (92) Chenitz et al. suggested some determinants of adherence to dialysis in the Philadelphia area, which included availability of transportation to and from the FHD centre, lack of motivation to attend dialysis and social factors taking priority. (93) These determinants may also be relevant to our study population. However, there are several unique factors about the treatment location (NT) of this study cohort. Australia's NT is a large, sparsely populated area. Many Indigenous patients are required to travel long distances from home communities to access haemodialysis. Visits home might, therefore lead to missing FHD sessions. For many Indigenous patients, attendance at dialysis may conflict with cultural and family obligations. Furthermore, reduced health literacy, different attitudes to "Western" medicine and the knowledge about the importance of regular attendance may also be limited, thereby leading to missing FHD sessions. Health Department sponsored transportation to and from the dialysis centre might be a solution for participants living near the centre. This arrangement does not alleviate the need for participants to relocate closer to a dialysis centre if such facility is not available locally. Substantial efforts have been made to improve access to dialysis for people in remote communities, including a visiting dialysis bus

service and installation of satellite FHD in many remote communities. (94, 95) Future studies including more recent data will help evaluate the effect of these interventions.

The lower likelihood of transplantation (and therefore placement on the transplant waiting list) among Indigenous participants in our study with dialysis attendance ≤2.5 sessions/ week is consistent with the opinions of the nephrologists in the national survey conducted in 2007. (83) Our findings confirm that the behaviour of nephrologists in practice is consistent with their stated survey responses. Among the US dialysis patients who missed dialysis, Gray et al. noted an increased risk for hospitalisation and deaths. (92) Because this outcome was not examined in our study, it is not known whether increased hospitalisation or death contributed to low rates of placement on transplant waiting list and transplantation.

In a review on kidney transplantation among Indigenous Australians with ESKD, Majoni et al. reported that practitioners concerns about the future behaviour of dialysis patients based on their dialysis attendance were controversial, especially given that follow-up and other requirements after kidney transplantation are very different to dialysis requirements. (96) Once participants (specifically those from remote locations) return home following kidney transplant, it would be much easier to plan and arrange travel to the specialists' appointments every 2-3 months as compared to attending FHD three times a week. Ongoing attendance at the FHD is perceived to be more burdensome than the ongoing follow-up after transplant. In the NT, participants from remote areas face forced relocation to the regional areas

where dialysis is available, while after receiving transplantation, they can return to their community. (79, 96)

Based on findings of Improving Access to Kidney Transplant (IMPAKT) study (10, 97, 98) and by Hughes et al., (79) which included the voice of Indigenous Australians with ESKD from the NT, transplantation is desirable among this patient population. Transplantation might provide an opportunity to return to the community and live with the family, improves emotional wellbeing and quality of life, and may act as an incentive for participants to look after their health. (79) The longer time spent on such a complex and strenuous treatment as haemodialysis may motivate the participants to look after their health following kidney transplants. The author agrees with the opinion of Majoni et al. (96) that "*patients missing dialysis because of the need to visit their communities for business issues requiring their presence such as funerals does not necessarily translate to poor adherence with medications after renal transplantation", and this* is contrary to the findings of the national survey (83) which indicated non-compliance as a reason for reduced numbers on the waiting list.

Because attending fewer than prescribed number of dialysis sessions is associated with increased mortality, strategies such as measures to increase awareness about dialysis and problems associated with non-attendance on dialysis are likely to result in good health while on dialysis. Good health while on dialysis may lead to an increased chance of placement on transplant waiting list and transplantation. Also, regular and repeated education about kidney transplant and what to expect after transplantation is likely to encourage dialysis patients to remain motivated through the process for

transplantation. Finally, early initiation of transplant assessment, at chronic kidney disease stage 4 where possible, is likely to reduce the transplant opportunities missed due to the increased numbers and severity of comorbidities as a result of a long duration of haemodialysis.

Implications of the study:

The likelihood of placement on transplant waiting list and transplantation for our study population was very low. Within the limitation of statistical power, it is established that ≤2.5 sessions/ week dialysis attendance is not related to graft loss following kidney transplantation. Therefore this should not be a determinant reason to not wait-list or not offer kidney transplantation. Rather than relying on the FHD attendance which was explored in this study, we recommend that future qualitative studies should focus on patients' perspective to understand the barrier to placement on the kidney transplant waiting list and kidney transplant. Such studies might allow a better understanding of additional issues around the reduced number of placement on the transplant waiting list and kidney transplants. Also, strategies to improve placement on transplant waiting list such as availability of pre-transplant work-up closer to the communities should be considered.

Similarly, evaluation of existing programs such as those utilising the role of Indigenous kidney transplant recipients in mentoring their peers receiving haemodialysis is likely to be helpful. Peers who have received transplantation can explain the processes and procedures in ways understandable and more relevant to the patients. Utilisation of such resources may then positively affect the chance of placement on the transplant waiting list and kidney transplantation.

There are limitations to this study. In addition to issues related to observational and retrospective nature of the data, small sample size limits the statistical power of the study. This is a problem inherent to our study population despite the inclusion of all Indigenous Australians with ESKD during the study period. The most critical issue is the very low rate of placement on the waitlist, and therefore very low numbers of endpoints. Finally, a key implication arising from this study is the need for further data. Our analysis used existing data. Our study described in chapter 2 indicated that the problems with placement on the transplant waiting list/transplantation facing Indigenous Australians with ESKD are not geographically restricted and are ongoing. Our study highlights the need for an updated analysis of current data to resolve the statistical issues that impact current practice.

Conclusion:

In the Northern Territory study cohort, rates of placement on the kidney transplant waiting list among Indigenous Australians with ESKD receiving FHD are low. FHD attendance ≤2.5 sessions/ week was associated with a reduced chance of kidney transplantation. In the study cohort, we did not find differences in kidney transplantation outcomes between different FHD attendance groups.

CHAPTER 4

Identification of risk factors predictive of good vs poor outcome following transplantation among Indigenous transplant recipients

Earlier in chapter 2, we discussed the known factors which are associated with graft and patient survival. Previous studies (11, 14, 75) have utilised information drawn from the Registry data. The registry data is limited in providing information on specific clinical and administrative factors at patient and hospital levels. The association between reasons for hospital admission pre-transplant, types of infection in cases of infection-related admissions, the severity of illness, length of hospital stay, discharge destination, the severity of comorbidities, and patient or graft survival are not known. Also, the association of types of immunosuppression, rejection and its management in the post-transplant period and patient or graft survival are unknown for Indigenous kidney transplant recipients.

Therefore, in following two studies we plan to investigate these associations in Indigenous kidney transplant recipients, how they compare in the pre-transplant and the post-transplant period and how they compare between those who have a functioning kidney transplant and those for whom their kidney transplant is not working. A cohort study was conducted to compare the factors in the pre and post-transplant period, and a case-control study has been chosen as the best way to efficiently gather more detailed information about an unusual event comparing those who have a functioning kidney transplant and those for whom their kidney transplant is not working. Given graft loss is an outcome with a long latency period; the case-control design allows exploration of risk factors within a logistically feasible number of subjects.

4.1 Pre and post-transplant hospitalisation among Aboriginal and Torres Strait Islander kidney transplant recipients

Synopsis:

Kidney transplant outcomes among Aboriginal and Torres Strait Island (Indigenous) Australians are poorer than their non-indigenous counterparts(12). This reflects an increased frequency of post-transplant infection, rejection and higher mortality rates among this group (14, 15). However, there is little information about hospitalisation rates and causes, a key marker of morbidity, in this group. In this study, we examined the hospital experiences of Indigenous kidney transplant recipients of South Australia (SA) and the Northern Territory (NT) in their two years pre-transplant and two years post-transplant period.

Objective: To compare the morbidity burden of infection and hospitalisation in the pre and post-transplant period among Aboriginal and Torres Strait Islander (Indigenous) kidney transplant recipients who underwent transplantation in South Australia (SA).

Design: A descriptive, retrospective cohort study was conducted. Data from hospital-based medical records, for Indigenous kidney transplant recipients from 1st January 2005 to 31st December 2015 was analysed.

Participants and Setting; All Indigenous kidney transplant recipients from all hospitals in SA and the Northern Territory (NT)

Main outcome measure: Rates of hospitalisation in the pre- and post-transplant period. Encounters for maintenance haemodialysis were excluded. Hospital admission rates including and excluding day admission for kidney biopsy or ureteric stent removal were presented separately.

Result: Eighty-nine transplants were performed among 88 recipients. The rate of hospital admission, excluding maintenance haemodialysis, was 2·4 (95% confidence interval (CI), 2·2, 2·7) per person-year in the pre-transplant period, 3·4 (95% CI, 3·0-3·8) in the first and 1·4 (95% CI, 1·1-1·6) per person-year in the second year post-transplantation. Rate of admissions with infection was higher in the post-transplant than the pre-transplant period, 1·6 (95% CI 1·4-1·8) vs. 0·6 (95% CI, 0·5-0·8) per person-year. The mean overall hospital days were longer in the two-year post-transplant compared with the pre-transplant period.

Conclusion: Length of hospital stay, rates of hospitalisation, and rate of admission with infection were high in the first year after transplantation, falling in the second year. A multifaceted approach to reduce the early excess morbidity burden after transplantation for this group is critical, including exploration of new clinical processes and identification of targeted areas for further study.

AJRH The Australian Journal of Rural Health
NATIONAL RURAL HEALTH ALLIANCE INC.

Pre and post-transplant hospitalisation among Aboriginal and Torres Strait Islander kidney transplant recipients

Journal:	*Australian Journal of Rural Health*
Manuscript ID	Draft
Manuscript Type:	Original Research
Keywords:	Aboriginal Health, epidemiology, indigenous health, chronic disease, clinical practice

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Setting: All Indigenous kidney transplant recipients from all hospitals in SA and the Northern Territory (NT)

Outcome measure: Rates of hospitalisation in the pre- and post-transplant period

Result: Of the 89 transplants among 88 recipients, 43 (49%) were from remote areas, and the majority were from the NT (88%). The rate of hospital admission, excluding maintenance haemodialysis, was 2·4 (95% confidence interval (CI), 2·2, 2·7) per person-year in the pre-transplant period, 3·4 (95% CI,3·0-3·8) in the first and 1·4 (95% CI,1·1-1·6) per person-year in the second year post-transplantation. Rate of admissions with infection was higher in the post-transplant than the pre-transplant period, 1·6 (95% CI 1·4-1·8) vs. 0·6 (95% CI, 0·5-0·8) per person-year.

Conclusion: Almost half of the study participants were from remote areas, and the majority were from the NT. Length of hospital stay, rates of hospitalisation, and rate of admission with infection was high in the first-year after transplantation, falling in

the second-year. The number of transplant recipients living in remote areas is steadily increasing, and their care is becoming an important facet of remote practice.

Keywords: chronic kidney disease (CKD), clinical epidemiology, clinical nephrology, registries, transplantation

What is already known on this subject:

- Improving kidney transplantation outcomes for Indigenous recipients is an agreed national priority.
- Indigenous transplant recipients from the remote areas have the highest chance of graft loss. Previous registry studies have shown higher mortality rates and increased graft loss as a result of post-transplant infection and rejection among this group.

What does this study add:

- The utilisation of hospital-level data showed increased hospitalisation rates in the post-transplant period with prolonged length of stay, increased need for ICU admissions and higher rates of admission where an infection was documented.
- The burden of hospitalisation was greater in the first year post-transplantation compared to the second year indicating that changes in strategies and protocols should focus in the first year post-transplantation.
- Our findings indicate these factors are likely predictors of poor outcome for Indigenous kidney transplant recipients, including those from remote and very remote areas. Furthermore, it provides areas to be addressed to improve the post-transplant outcome for Indigenous recipients.

Introduction:

Except for dialysis outcomes, which are comparable between the Indigenous and non-Indigenous end stage kidney disease patients, Indigenous Australians have worse outcomes for kidney transplantation. [1, 2] The disparity is more pronounced among the Indigenous transplant recipients from rural areas as compared to the Indigenous recipients from the major cities and inner regional areas. [2] Higher rates of deaths due to infection may explain decreased rates of graft and patient survival in Indigenous kidney transplant recipients; with the risk highest from 6 to 24 months post-transplantation. [3] Previous studies using registry data have focused on graft function and mortality. [2-5]

Registry data is broad, but it lacks depth and hospital-level details. There is little information about hospitalisation rates and reasons for hospitalisation, which are key markers of morbidity for Indigenous Australians. In this study, we explored this issue in detail using hospital-level data about Indigenous kidney transplant recipients from South Australia (SA) and the Northern Territory (NT) in their two years before and after transplantation.

Methods

All Indigenous kidney transplant recipients who received a kidney transplant through the SA/NT kidney transplant service from 1 January 2005 to 31 December 2015 were included. This service is based in SA and provides kidney transplantation to individuals throughout SA and NT. This includes end stage kidney disease (ESKD) patients from all remoteness categories referred from the Royal Darwin Hospital Alice Springs Hospital Central and Northern Adelaide Renal and Transplant Services and the Flinders Medical Centre. Data on patient admissions were taken from hospital records. This included the frequency and duration of hospital admissions, reason for each admission as documented in the discharge summary or the progress notes when the summary was missing, laboratory and radiologic investigations, date of discharge following each admission, pre-transplant investigation results, transplant events, transplant kidney biopsy results and drug levels. Information was obtained for the two years pre-transplant, peri-operative and post-transplant periods for the participants included. The ‘index admission’ for transplant surgery (‘peri-operative period’) was defined as the period from the day that the participant was admitted to

the hospital for the transplant operation until discharge for the first time post-transplant surgery. Hospital-based electronic and hard copies of patients' medical records were reviewed. Where applicable, information was cross-checked with data on Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Data from the registry were utilised where data were missing from the hospital records.

The hospital admission rate was defined as the number of hospital admissions per person-year. Patients were followed-up on for two years post-transplant or death, whichever occurred first-only hospital encounters for maintenance haemodialysis in both pre- and post-transplant periods were excluded. An infection episode was defined as a hospital admission in which any infection was documented during the admission by either the results of the investigation or if the diagnosis given by the treating team was labelled as infection-related.

The coronary angiogram results were categorised based on the cardiologist's interpretation provided in the report. The results were categorised as abnormal if the cardiologist's report mentioned the involvement of any number of coronary arteries and reported other than a minor disease. Delayed graft function was defined as requiring dialysis in the first-week post-transplantation.

Remoteness was determined using the Australian Bureau of Statistics (ABS) categories based on the postcode of residence. [6] The time taken to return to the referring hospital was calculated as the time from transplant to the first encounter at the referring hospital (where the referring hospital was different from the transplanting hospital). The date of return to the remote community was considered either the actual date documented when the participant returned to the community with a functioning transplant or the date of attendance of the last clinic visit when an intention to return to the community was noted and was accompanied by indirect evidence of community residence (e.g., a blood test taken in the community or presentation to the community hospital).

Frequencies and proportions were calculated for each variable. Data were analysed using Stata 15 (College Station, TX).

This study was approved by the Office of Research Ethics, Compliance and Integrity Research Services, the University of Adelaide; Human Research Ethics Committee

of the Northern Territory Department of Health and Menzies School of Health Research; Central Australian Human Research Ethics Committee; Royal Adelaide Hospital Central Adelaide Local Health Network Human Research Ethics Committee; Flinders Medical Centre South Adelaide Local Health Network Human Research Ethics Committee; and the Aboriginal Human Research Ethics Committee, SA.

Results: Cohort characteristics

A total of 88 participants met the inclusion criteria, their baseline characteristics and those of the transplants are presented in Table 1a and 1b, respectively. Participants from the NT made up the majority of the study population. Forty-three (49%) of the transplant recipients were from the remote areas (ABS 'Remote and Very Remote' classifications), and the majority 38 (88%) were from the NT. The proportion of participants from remote areas was higher in the NT group than the SA group (76% vs 11%). There were more male participants than female participants. The median age at the start of renal replacement therapy (RRT) was 43·5 years (Interquartile ratio [IQR], 35, 49) and the median age at the time of transplantation was 47 years (IQR, 41, 55). Twelve deaths (13·5%) occurred within two years of transplantation, of which 7 (58·3%) were in the first year post-transplant, including three deaths during the index admission.

Of 277 post-transplant biopsies performed (excluding 80 implantation biopsies) on 89 transplants, 95 (34·3%) had histopathologically established acute rejection, including both cellular and vascular rejection. The indication for 67/277 (24·2%) of biopsies was recorded as 'protocol'. Of the protocol biopsies, six (8·9%) biopsies revealed some form of acute rejection. Information on specific treatment was available for 76 (80%) of the 95 biopsies performed for rejection episodes; of these 51 (67·1%) had an escalation of immunosuppression, and 19 (25%) received anti-thymocyte globulin alone or in combination with other changes in maintenance immunosuppression for the treatment of rejection. For 20% of episodes, information on treatment for rejection was missing in both the hospital file and the registry database.

The two-year pre-transplant period

A total of 431 hospital admissions were recorded for 80 participants during the two-year pre-transplantation period. The remaining eight participants had no hospital admissions during this period. The hospital admission rate one to two years pre-transplant was similar to the year immediately pre-transplant (2·3 per person-year (95% CI, 2·0-2·7) vs. 2·5 per person-year (95% CI, 2·2-2·9)). The median number (IQR) of days spent in the hospital in the two-years pre-transplant period was 16·5 (7·0-35·5) days per person.

Index admission for transplant surgery(peri-operative period)

There were 89 kidney transplant operations performed during the study period (Table 2). One participant received two kidneys within the study period. Of the 89 transplants, eight (9·0%) were second grafts. Table 2 shows the details of the admission episode for the transplant operations; the median length of stay was nine (IQR 7, 12) days, with 11% requiring admission to the intensive care unit during admission for transplant surgery, with a median length of stay in the intensive care unit of one day (IQR, 1, 4). The median total ischaemia time was 16·5 hr (IQR 13–21), and delayed graft function requiring dialysis occurred in 52% of transplants.

Post-transplant period

There were 779 hospital admission episodes in the two-year post-transplant period. The majority (53·2%) of the hospital admissions in the post-transplant period were day admissions for graft biopsy or ureteric stent removal. Excluding day admissions, the hospital admission rate in the two years post-transplant was 2·4 per-person year (95% CI, 2·2-2·7); 3·4 (95% CI, 3·0-3·8) per person-year in the first 12 months after transplantation falling to 1·4 (95% CI, 1·1-1·6) per person-year in the second year. Thirty-six episodes (5.6%) of the hospital encounters were recorded as the presentation at a rural hospital; details of these encounters were unavailable. Figure 1 shows the mean length of stay in pre and post-transplant period and the first and second-year post-transplantation., while Table 3 shows the overall hospital admission data for the pre and post-transplant period.

Figure 2 shows the time taken in days for the participants to return to the referring hospital not counting for those referred from within the transplanting hospital. The

median time to return to the referring hospital was 38 days (IQR, 30–49). The majority of patients returned 21–56 days post-transplantation. Data on the return of participants from areas other than major cities to their community residence (n = 70) were only available for 39 (55·7%) of the study participants. Of these 39, two (5·1%) returned within four weeks of transplant surgery, 12 (30·8%) returned within four to eight weeks, and 25 (64·1%) returned after more than eight weeks.

Details of admissions in which infection was documented

The rate of admissions in which infection was documented was higher in the post-transplant period at 1·6 (95% CI 1·4-1·8) vs. 0·6 (95% CI 0·5-0·8) per person-year in the pre-transplant period. The rate of admissions in which infection was documented was higher in the first-year post-transplant period compared with the second-year post-transplant period, with 2·3 (95% CI, 2·0-2·7) vs. 0·9 (95% CI, 0·7-1·2) episodes per person-year. Figure 3 and the Appendix table i provide details on admissions in which infection was documented in the pre- and post-transplant period.

Of the 69 participants in whom infection was documented during at least one of the post-transplant hospital admissions, the biopsy-proven rejection was documented in 37 (53·6%) participants, and an escalation of immunosuppression was recorded in 33 (47·8%) participants. Data on the treatment of rejection were not available for four (10·8%) of the 37 participants with biopsy-proven rejection. Of the 37 participants with biopsy-proven rejection, 31 (83·8%) had an escalation of immunosuppression before admission episode in which infection was documented.

Out of 274 admission episodes in which infection was documented, 105 (38·3%) episodes happened after an escalation of immunosuppression for biopsy-proven rejection. Seventy (66·7%) of the 105 episodes occurred in the first year post-transplantation. The rate of hospital admission episodes in which infection was documented with an escalation of immunosuppression was 0·5 (95% CI, 0·3-0·7) per person-year. This was similar to the admission rate among patients without an escalation of immunosuppression, and the incidence rate ratio was 1·1 (95% CI, 0·7-1·8)). Appendix Table ii lists the types of infection documented during admission after an escalation of immunosuppression.

The vast majority of participants were cytomegalovirus (CMV) immunoglobulin (Ig) G, Epstein–Barr virus (EBV) IgG and Varicella zoster virus (VZV) IgG-positive pre-transplant. A positive blood CMV polychromatic chain reaction PCR result was recorded in 42 (47·2%) participants on at least one occasion in the two-year post-transplant period. Similarly, 19 (21·4%) had at least one documented positive blood BK virus PCR result.

Pre-transplant latent tuberculosis (TB) was detected in 13 (14·6%) of the 89 transplants. For participants at low risk for TB (n=55), screening for TB was not performed. All cases of latent TB completed treatment with isoniazid for nine months pre-transplant. There were no cases of TB two years post-transplantation in this group. Pre-transplant screening test results are presented in Appendix Table iii.

Discussion

Kidney transplantation offers an advantage in survival, quality of life and cost compared with dialysis across a variety of groups. [7-9] However, graft loss is highest among the Indigenous transplant recipients from the remote areas. [2] Improving the rate of kidney transplantation and graft and patient survival among Indigenous end-stage kidney disease patients is an agreed national priority in Australia. [4, 5, 10] Inclusion of almost half of the participants from the remote areas meant the findings from the study is relevant for transplant recipients from rural Australia.

Our study extends previous data and records a high morbidity burden, particularly in the first year after transplantation. This illustrates a critical need to focus on the early post-transplantation period and examine measures that can reduce hospitalisations, and in particular infections. This burden of morbidity also manifests itself in long hospital, and intensive care unit stays in the post-transplant period (particularly in the first year post-transplant). Falling admission rates in the second year post-transplantation are encouraging and suggest that the longer-term admission rate should be investigated further in future studies.

More than half the kidney transplant recipients in the present study cohort had some form of biopsy-proven acute rejection episode at least once in the two-year post-transplant period. Day hospital admissions for graft biopsy and ureteric stents removal add enormous pressure on both the patients and the hospital. Patients are required to make multiple adjustments to their everyday schedule to attend for the procedure and post-procedure care. For patients living in remote areas, these admissions carry the burden of travel to a major centre for hospitalisation. One day-procedure in the regional or tertiary care centre may mean finding someone to accompany them to their treatment, arriving a day before and leaving a day later from the city, potentially consuming at least six person-days away from the community. Some post-transplant encounters occurred at a rural hospital, while details of these encounters were unavailable because the medical records were reviewed at a referral centre, this emphasises the importance of ongoing education of rural hospital staff.

The excess infection rate likely reflects both the underlying rates of infection seen among the general (non-dialysis) Indigenous population and the effect of

immunosuppression. For the general population, the rate ratio for hospitalisation due to infection in SA and NT between the Indigenous and non-Indigenous from June 2013–2015 was 1·9 and 3·5, respectively. [11] Admission rates were particularly high among Indigenous Australians living away from major cities. [11] Such areas also have higher rates of end-stage kidney disease and transplantation. General measures to reduce the prevalence of infection in remote communities, therefore, are particularly relevant to this group.

There was a close nexus between the high frequency of infection and the burden of immunosuppression in the first year. The relationships between immunosuppression, infection and rejection are complex. While cause and effect between these factors may be difficult to discern in some cases, the data recorded in the present study suggested that a reduction in immunosuppression due to infection was a major contributor to the increased rate of rejection.

Treatment of BK and CMV viraemia requires a reduction of immunosuppression, which increases the chance of rejection and graft loss. Current protocols include valganciclovir prophylaxis for those at high risk of CMV and regular screening for BK viraemia. At present, there is no established prophylaxis for the prevention of BK virus infection, which could be considered in high-risk cases. [12] Alternative approaches, such as ongoing antiviral use for CMV and longer-term or indefinite viral screening for both CMV and BK virus, should be examined for this group. Further, differing approaches to organ allocation, such as utilising eplets rather than HLA matching, may help resolve the underlying issues of immunosuppression vs infection. [13, 14] Donor BK virus screening may also help stratify high-risk recipients, though such data are not currently available for Australian donors. [15, 16]

The ability to return to the community is a major benefit of transplantation. Previous studies have highlighted the importance of being able to remain close to family and stay in the community for Australian Indigenous patients on dialysis. [17] Transplantation can allow recipients to return to the community and country. Unfortunately, in the present study, the data available on return to the community were incomplete. The available data suggested that the majority of patients took longer than eight weeks to return home. Whether this prolonged interstate stay for

transplant surgery discourages patients from opting for transplantation requires further evaluation.

Our study has some limitations. First, the study sample was relatively small, despite the inclusion of all transplants performed over this period. Data on the treatment of rejection and the immunosuppressant blood levels were incomplete, though the proportion of missing data was similar to that of the registry data on the treatment of rejection. The discharge destination and dates of discharge to the community were extrapolated from the indirect information available in the hospital records. Follow-up information confirming participants' departure to their communities was used to ensure the accuracy of the dates as best possible. However, it should be noted that the information on the participants' return to their referring centres was accurate.

Successful transplantation can reduce the burden of remoteness by facilitating the treatment of people from remote areas in the community. This report identified several challenges and areas for improvement that can be divided into a) transplant and person-specific factors and b) general or community-related factors.

a) Transplant and person-specific factors include frequent hospital admissions, extended hospital stay and increased rate of infection, all of which exposed participants to acute and chronic consequences, such as physical and emotional stress and increased graft loss in the post-transplant period. Such factors also meant that participants were away from home for a longer time. Areas for improvement include broader or prolonged post-transplant prophylaxis (non-nephrotoxic antifungals, as recommended for lung, liver and small bowel transplants) for fungal and viral (e.g., a mandatory continuation of valgancyclovir for one year or more) infections. In cases where repeated staphylococcus aureus infections occur, decolonisation to reduce the burden of skin pathogens may be considered, as recommended for the general population who present with recurrent abscess. [18, 19]

Technological advances that reduce the possibility of delayed graft function and measures that reduce travel time to the transplanting hospital will also help improve postoperative morbidity and graft outcomes. At present, studies examining the pharmacodynamics and pharmacokinetics of immunosuppression in Indigenous Australians to identify appropriate drug dosing protocols, as well as studies exploring

epitope matching, are underway. The extent to which an earlier return home is feasible will vary between people and communities; reducing the high burden of infection and hospitalisation is an important facilitator of this.

b) Community and general factors: in general, improving access to appropriate housing and health-promotion interventions in the community, including hand hygiene, are likely to reduce overall community infection rates. [20, 21] Whether these measures are important from a kidney transplant perspective is yet to be conclusively shown, but is likely. Improved data-keeping of information such as time to return the community will allow for the measuring of important patient-relevant measures such as those outlined above.

Conclusion:

Our study demonstrated increased morbidity and mortality in the post-transplant period, particularly in the first year post-transplantation. Reducing early excess morbidity after kidney transplantation for these patients is critical, so they can avail the benefits of this treatment while continuing to live in the country. Management protocols that aim to reduce the risk of acute rejection, prevent infection in the post-transplant period and enable participants to return home should be prioritised. Studies exploring the role of broader prophylaxis may help reduce future infections. Further research is required to explore the inter-relationship between levels of immunosuppression and the occurrence of infection, and the relationship of these findings with graft and patient outcomes. It is important to note that, almost half of the study participants were from remote areas, and the majority were from the NT. Improvements in provision of dialysis and transplant services in rural and remote areas mean the number of dialysis and kidney transplant recipients living in these areas is steadily increasing, and care for this group is becoming an important part of remote practice.

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Baseline characteristics of participants	Value
N	88
Residential state	37 (42%)
South Australia	
Northern Territory	51 (58%)
Remoteness	
Remote/ Very- remote Areas: South Australia	11%
Remote/ Very- remote Areas: Northern Territory	76%
Age at RRT initiation, median (IQR*)	43·5 (35·5, 49)
Gender	
Female	39 (44%)
Chronic lung disease at RRT^ start	6 (7%)
Spirometry	
Abnormal- ¶FEV:FVC 60-69%	5 (6%)
Normal- FEV:FVC >=70%	83 (94%)
Coronary artery disease at RRT start	21 (24%)
Coronary Angiography	
Normal	18 (20%)
Minor disease	17 (19%)
Abnormal	26 (30%)
Not Performed	20 (23%)
Missing	7 (8%)
Diabetes	
Type 1 or Type 2	53 (60%)
Cerebrovascular disease at RRT^ start	4 (5%)
Peripheral vascular disease at RRT^ start	9 (10%)
Death within 2 years Post-transplant	12 (13·6%)

Table 1(a): Baseline characteristics of the study participants.

* IQR- Inter-quartile range ^ RRT- Renal replacement therapy ¶ FEV1- Forced expiratory volume in 1 minute, FVC- forced vital capacity

Baseline characteristics of transplants	N=89
Donor source- Deceased	89 (100%)
Age at transplant, median (IQR)	47 (41, 55)
Number of first transplant	81 (91·1%)
Donor age, median (IQR)	47 (36, 61)
Donor gender	
Female	47 (53%)
Total ischaemia time (hrs), median (IQR)	16·5 (13, 21)
Delayed graft function	
Not requiring dialysis	42 (47%)
Delayed Graft Function requiring dialysis	46 (52 %)
Missing information	1 (1%)
Total ischaemia time, categorised	
Total ischaemia time <16 hours	40 (44·9%)
Total ischaemia time >16 hours	49 (55·1%)
Initial Immunosuppression	
Basiliximab Tacrolimus Mycophenolate Prednisolone	72 (80·9%)
Others including trials and Anti-Thymocyte globulin	17 (19·1%)
Rejection	
No rejection	42 (47·2%)
At least one episode of any rejection	47 (52·8%)
Vascular rejection episodes per-participant in 2 years	
One episode	22 (24·7%)
2 or more	12 (13·5%)
Cellular rejection episodes per participant in 2 years	
One episode	26 (29·2%)
2 or more	19 (21·4%)
Received ATG* for rejection	17 (19·1%)
HLA-A^ mismatch- *none*	6 (7%)
One HLA mismatch	30 (34%)
Two or more	53 (60%)
HLA-B^ mismatch- *none*	5 (6%)
One HLA mismatch	16 (18%)
Two or more	68 (76%)
HLA-DR^ mismatch- *none*	7 (8%)
One HLA mismatch	24 (27%)
Two or more	58 (65%)
HLA-DQ^ mismatch- *none*	12 (38%)
One HLA mismatch	15 (47%)
Two or more	5 (16%)

Table 1 (b): Characteristics of the kidney transplants.

*ATG- Anti-thymocyte globulin ^ HLA- Human leucocyte antigen

Admission for Transplant Operation	Value
N	89
Total inpatient days for transplant surgery, mean (95% CI) days	14 (95% CI, 10·8-17·2)
Total LOS in ICU during Transplant surgery, median (IQR)	1 (1, 4)
Frequency of total ICU admissions immediate Post-transplant period	
1 episode of ICU admission	10 (11%)
>1 episode of ICU admission	1 (1%)
Complication* during the hospital stay	60 (67%)
Peri-transplant Discharge destination	
Hostel	63 (71%)
Home	23 (26%)
Death	3 (3%)
Discharge creatinine (excluding dialysis dependant at discharge), µmol/l, median (IQR)	224 (122, 490)
Was an infection documented during this admission	
Any infection documented	41 (46%)
Type of infection immediate post-transplant (peri-op)	
Bacterial	26 (29%)
Mixed- a combination of Bacterial, Viral, Parasitic and Fungal	12 (14%)
Fungal	3 (3%)
Source of infection	
Respiratory	3 (3%)
Urine	9 (10%)
CVC-PD	3 (3%)
Miscellaneous- including wound, perfusion fluid, gastrointestinal & multiple sites	26 (29%)

Table 2: Characteristics of the hospital admission for kidney transplant surgery

*Complication: any surgical or medical complication documented as “Yes” in the section to mark complication in a discharge summary

	Pre-transplant period	Post-transplant period	P-value
Total number (N)	89	86	
Inpatient hospital episodes in 2 years	431	779	
Hospital admission rate (per person-year)	2·4 (95% CI, 2·2-2·7)	4·5 (95% CI, 4·2-4·9)	0·0
Overall rate of admission (per person-year)			
up to 1 year		6·8	
1-2 year		2·1	
Incidence rate ratio for 1: 1-2 year		3·2 (95% CI 2·7-3·9)	0·0
Day admission	199 (46·2%)	365 (46·9%)	0·8
Total inpatient days per participant in 2 years, median (IQR)[#]	6·5 (1·5, 15·5)	14 (5·5, 44·5)	
Frequency of Admissions per participant in the study period			
One or less than one (≤1)	21 (23·6%)	2 (2·3%)	0·0
Two to three (2-3)	25 (28·1%)	13 (5·1%)	0·0
More than three (>3)	43 (48·3%)	71 (82·6%)	0·0
Total LOS in ICU[¶] at any time 2 years, median (IQR)	2 (1, 4)	7·5 (3·5, 26)	
Total ICU[¶] admission episodes	13 (0·3%)	23 (2·9%)	0·0
Frequency of ICU[¶] admission within each hospital admission episode			
1	13 (100%)	5 (21·7%)	
2		6 (26·1%)	
3 or more		12 (52·2%)	
Proportion of admission episodes where an infection was documented	112 (25·9%)	274 (35·2%)	0·0
Incidence rate of infection (per person-year)	0·6 (95% CI, 0·5, 0·8)	1·5 (95% CI, 1·4, 1·7)	0·0
Discharge destination for each inpatient encounter			
*Home with or without HITH**	229 (52·2%)	324 (41·3%)	0·0
Hostel	44 (10·0%)	191 (24·3%)	0·0
Other	20 (4·6%)	55 (7·0%)	0·1
Missing	146 (33·3%)	215 (27·4%)	0·0

Table 3: Hospital admission and discharge information in the pre and post-transplant period.

*HITH – Hospital in the home ¶ ICU- Intensive care unit # IQR- Interquartile range

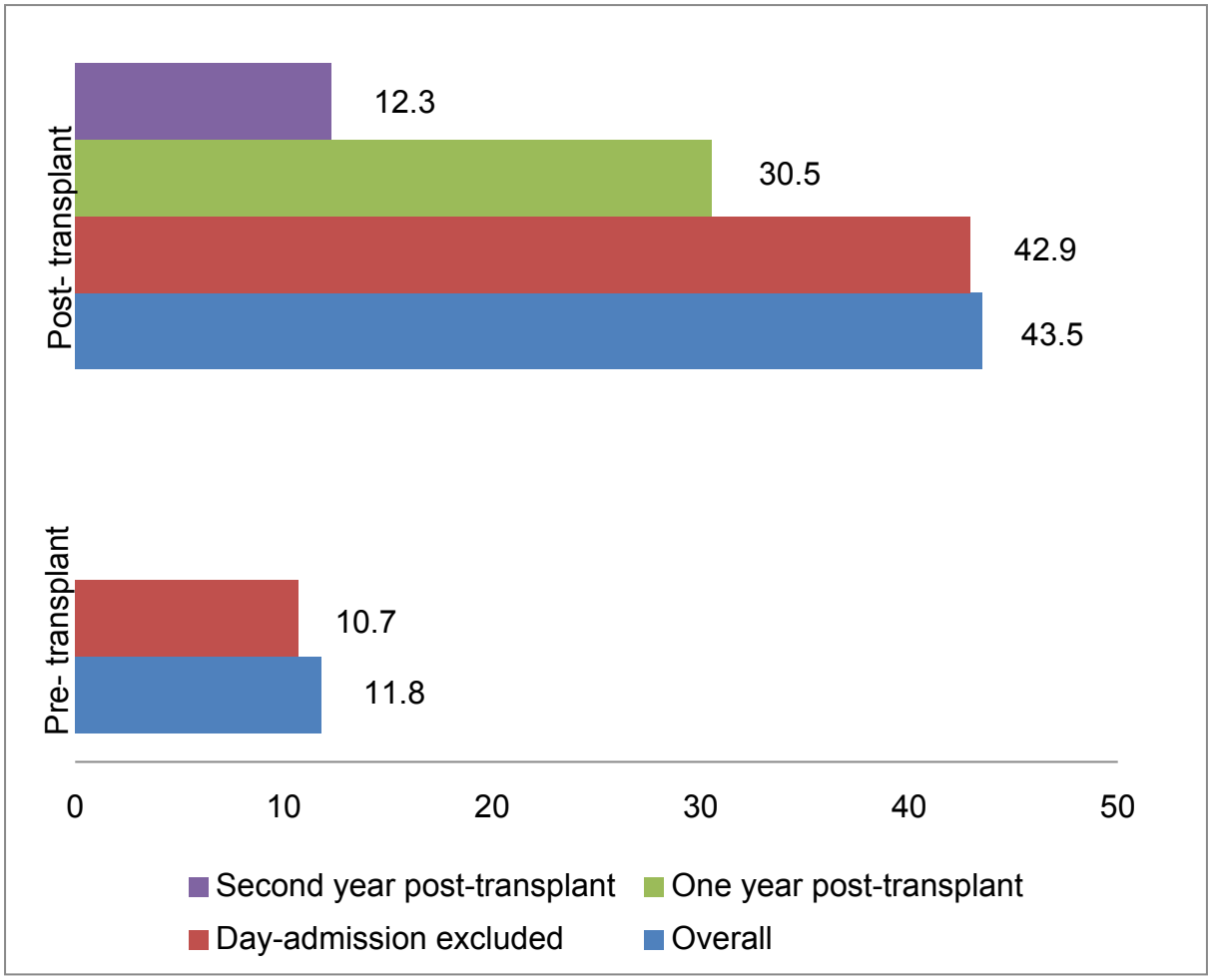

Figure 1: Mean total length of inpatient stay (in days) in pre and post-transplant period; overall length of stay includes day admission during these periods.

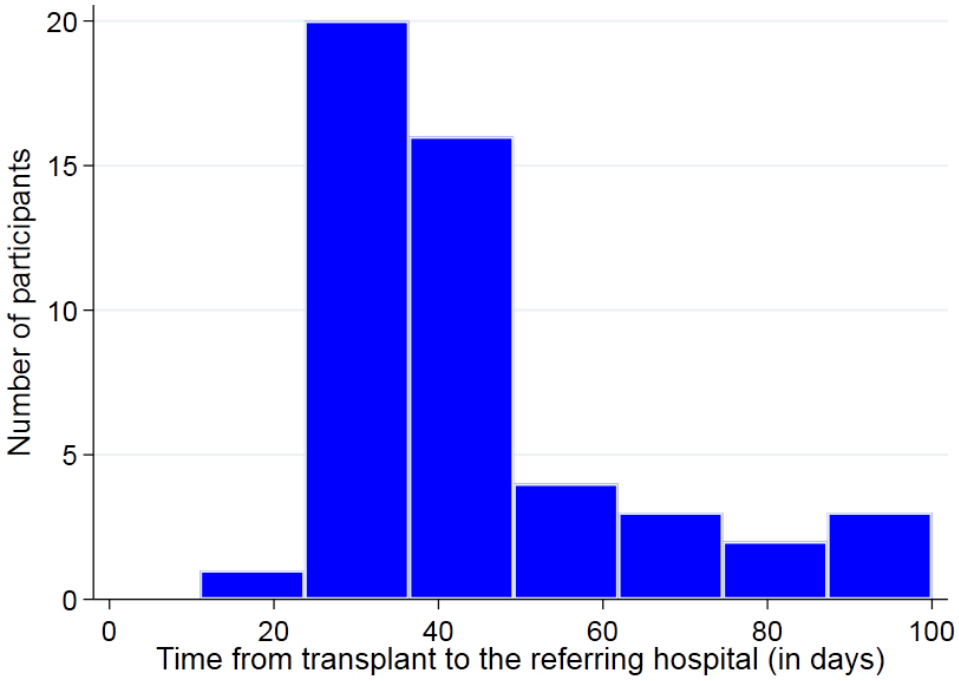

Figure 2: Time from transplant to the referring hospital

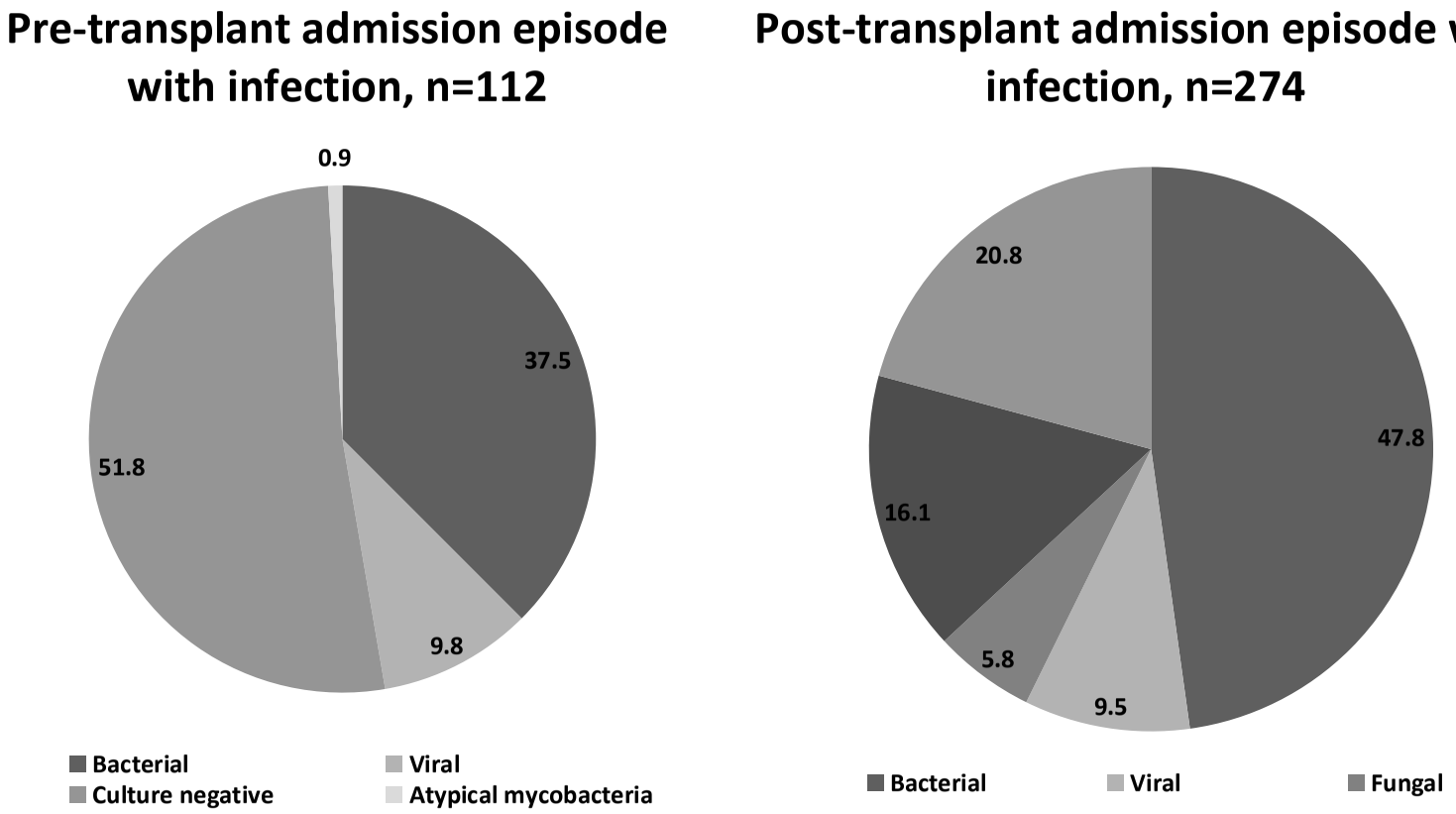

Figure 3: Details of pre and post-transplant infection

Appendix i:

	Pre-Transplant	Post-Transplant	P-value
Total admission episodes	N=431	N=779	
Total number of admission episodes in 2 years where Infection was documented	112 (25.9%)	274 (35.2%)	0.0
Incidence rate ratio for admissions with infection in the first and second-year post-transplant period	2.5 (95% CI, 1.9, 3.3)		0.0
Infection in the first year post-transplant (of the total inpatient episodes in 1st year, n=599)		199 (33.2%)	0.0
Infection in the second year post-transplant (of the total inpatient episodes in 2nd year, n=180)		75 (41.7%)	
Incidence rate ratio for post and pre-transplant hospital admission episodes with infection	2.6 (95% CI 2.1-3.2)		0.0
Type of infection among the episodes where an infection was documented			
Bacterial	42 (37.5%)	131 (47.8%)	0.1
Viral	11 (9.8%)	26 (9.5%)	0.9
Fungal		16 (5.8%)	0.1
Polymicrobial		44 (16.1%)	
Others (including Culture negative) *	59 (52.7%)	57 (20.8%)	
Source of infection			
Respiratory	41 (36.6%)	46 (16.8%)	0.0
Gastrointestinal	16 (14.3%)	32 (11.7%)	0.4
AVF-CVC-PD	28 (25%)		
Miscellaneous-including skin, urine, multiple sites	37 (24.1%)		
Miscellaneous-including skin, multiple sites		82 (29.9%)	
Genitourinary		86 (31.4%)	
Missing		28 (10.2%)	
Infection Episodes in category (out of the total number of admission episodes)			
Infection episode=1	23 (5.3%)	21 (2.7%)	0.0
Infection episode >1	89 (20.7%)	253 (32.5%)	0.0

Table i: Details of pre and post-transplant infection

*includes fungal and polymicrobial infection for the pre-transplant period- categories combined to improve statistical power. Proportion comparison combined fungal and polymicrobial with others for the post-transplant period

Appendix ii:

Type of Infection, Post-Transplant	Frequency	Per cent
Bacterial	36	34.29
Viral	12	11.43
Fungal	6	5.71
Polymicrobial- Bacterial &/or Viral &/or Fungal	17	16.19
Culture negative	34	32.38
Type of Infection, Post-Transplant	Frequency	Per cent
Bacterial	36	34.29
Viral	12	11.43
Fungal	6	5.71
Polymicrobial- Bacterial &/or Viral &/or Fungal	17	16.19
Culture negative	34	32.38

Table ii: type of infection in the admission episodes after the escalation of immunosuppression

Appendix iii:

Total transplant episodes	N=89
Pre-transplant Varicella	84 (94%)
Pre-transplant CMV	87 (98%)
Pre-transplant EBV	87 (98%)
Pre-transplant HTLV*	4 (4%)
Pre-transplant HIV (negative)	89 (100%)
Pre-transplant Hepatitis C	4 (4%)
Pre-transplant Hepatitis B	2 (2%)
Pre-transplant Strongyloides*	10 (20%)
Pre-transplant Treponema Pallidum*	15 (29%)
Latent Tuberculosis*	30 (34%)
Toxoplasma	20 (22%)

Table iii: Infection screening pre-transplant

*tested in high-risk groups only

4.2 A retrospective case-control study exploring factors for loss of kidney transplant function or death among indigenous kidney transplant recipients

Synopsis:

Survival after kidney transplantation is poor among Australian Aboriginal and Torres Strait Islanders (hereafter referred to as Indigenous Australians) when compared to non-indigenous kidney transplant recipients(12). When compared to their non-indigenous counterparts, deaths due to infectious diseases were substantially higher among Indigenous kidney transplant recipients in all of Australia (99).

A retrospective case-control study was conducted, to identify risk factors for graft and patient survival among Indigenous kidney transplant recipients, beyond the information available from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.

Methods

Cases were defined as all Australian Indigenous kidney transplant recipients from 1st January 2005 to 31 December 2015 from the major hospitals in the Northern Territory (NT) and South Australia (SA) who experienced graft loss (including patient death) up to 2 years post-transplant. Controls (matched 4:1) were defined as all Indigenous kidney transplant recipients during the same period, from same locations with functioning kidney transplant at two years post-transplant operation. Matching was done on gender and presence or absence of diabetes status. The analysis was adjusted for age at kidney replacement therapy (KRT) start. Hospital-level data was linked with the data in the ANZDATA registry, and comparison was made between

cases and controls. Post-transplant hospital admission rate excluded day admissions such as admissions for transplant biopsy and ureteric stent removal.

Results

There were 17 cases and 68 matched controls. Among the cases, odds ratio (OR) for more than one hospital admission episode (compared to ≤1 episode) in the two years pre-transplant period was 6.2 (95% CI, 1.2- 32.5). However, there were no significant differences in the frequency of comorbidities at KRT start, cardiovascular intervention pre-transplant, pre-transplant infection screening, age and gender of the donors, frequency of admission episodes where an infection was documented, the total length of inpatient stay or admission to intensive care unit (ICU) during pre-transplant hospital admission between cases and controls.

Conclusion:

Early loss of graft was predicted by a higher frequency of hospital admissions in the two-year pre-transplant period. In contrast, other measured factors in the pre-transplant period did not predict these adverse outcomes.

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

A retrospective case-control study exploring pre-transplant predictors for loss of kidney transplant function or death among Indigenous kidney transplant recipients

Journal:	*Clinical Transplantation*
Manuscript ID	Draft
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	n/a
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Discipline:	kidney transplantation/nephrology, outcomes research/registry studies, infectious disease
Keywords:	clinical decision-making, complication, ethnicity / race, graft survival, kidney (allograft) function / dysfunction
Abstract:	A retrospective case-control study was conducted, to identify risk factors for loss of kidney transplant function or death among Indigenous kidney transplant recipients. Methods Cases were defined as all Australian Indigenous kidney transplant recipients from 1st January 2005 to 31st December 2015 from the major hospitals in the Northern Territory (NT) and South Australia (SA) who experienced graft loss (including patient death) up to 2 years post-transplant. Controls (matched 4:1) were defined as all Indigenous kidney transplant recipients during the same period with functioning transplants at two-years post-transplant operation. Matching was done on gender and diabetes status. Cases and controls were compared using regression analysis adjusted for age. Results There were 17 cases and 68 matched controls. Among cases, odds ratio (OR) for more than one hospital admission episode (compared to ≤1 episode) in the two years pre-transplant period was 6.2 (95% CI, 1.2-32.5). However, there were no significant differences in other measured comorbidities between cases and controls. Conclusion Early loss of graft was predicted by a higher frequency of hospital admissions in the two-year pre-transplant period. Future policies should address broader social determinants of health to improve pre-transplant health and thus improve the potential for optimal post-transplant outcomes.

A retrospective case-control study exploring pre-transplant predictors for loss of kidney transplant function or death among Indigenous kidney transplant recipients

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Running Title: Indigenous kidney transplant recipients

A retrospective case-control study exploring pre-transplant predictors for loss of kidney transplant function or death among Indigenous kidney transplant recipients

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Abstract:

Background

A retrospective case-control study was conducted, to identify risk factors for loss of kidney transplant function or death among the Indigenous kidney transplant recipients.

Methods

Cases were defined as all Australian Indigenous kidney transplant recipients from 1st January 2005 to 31 December 2015 from the major hospitals in the Northern Territory (NT) and South Australia (SA) who experienced graft loss (including patient death) up to 2 years post-transplant. Controls (matched 4:1) were defined as all Indigenous kidney transplant recipients during the same period with functioning transplants at two-years post-transplant operation. Matching was done on gender and diabetes status. Regression analysis adjusted for age was used for comparing cases and controls.

Results

There were 17 cases and 68 matched controls. Among cases, odds ratio (OR) for more than one hospital admission episode (compared to ≤1 episode) in the two years pre-transplant period was 6.2 (95% CI, 1.2- 32.5). However, there were no significant differences in other measured comorbidities between cases and controls.

Conclusion

Early loss of graft was predicted by a higher frequency of hospital admissions in the two-year pre-transplant period. Furthermore, broader social determinants of health should be addressed in order to improve pre-transplant health and thus improve the potential for optimal post-transplant outcomes.

Keywords: Kidney allograft function/dysfunction, graft survival, ethnicity, complication, clinical decision-making

Introduction

For the majority of people with end-stage kidney disease (ESKD); when compared to dialysis, kidney transplantation offers an advantage in survival and cost. Transplant recipients can also expect a better quality of life. [1, 2] Nevertheless, the rate of kidney transplantation among Australian Indigenous end stage kidney disease (ESKD) patients is substantially lower, and differences persist in graft and patient survival. [3-5] The majority of deaths among kidney transplant recipients are due to cardiovascular diseases, cancer and infectious diseases[6]. Higher rates of deaths due to infection may explain decreased rates of graft and patient survival in the Indigenous kidney transplant recipients; with the risk highest from 6 to 24 months post-transplantation. [7] Previous studies have utilised information drawn from the Registry data. [3, 4, 7] However, the registry data is limited in providing information on specific clinical factors at the patient and hospital levels. The association between reasons for hospital admission pre-transplant, types of infection in cases of infection-related admissions, the severity of illness, length of hospital stay, discharge destination, the severity of comorbidities, and patient or graft survival are not known.

In this study, we aim to identify the pre-transplant risk factors for early graft loss and death among Indigenous kidney transplant recipients. To explore the predictors of this outcome, we conducted a retrospective case-control study to examine possible risk factors.

Methods:

Study population and data source: Australian Indigenous kidney transplant recipients from 1st January 2005 to 31st December 2015 from the major hospitals in the Northern Territory (NT, Alice Springs Hospital and Royal Darwin Hospital) and South Australia (Central and North Adelaide Renal Transplantation Services and Flinders Medical Centre) were identified from the ANZDATA Registry. At each hospital, medical records for these participants were audited. Information was collected on the dates of admission and discharge, frequencies of hospital admissions, the reason for each admission as documented in the discharge summary or from the progress notes where such a summary was missing, laboratory and radiologic investigations, pre-transplant screening investigation results, and details of pre-transplant cardiovascular intervention. Information was obtained for the two years pre-transplant on the included participants. Hospital-based electronic and hard copies of the medical records were reviewed. Where the data was missing from the hospital records, then the data from the ANZDATA registry was utilised if available.

Cases were selected from the cohort of included participants (described above) and defined as those who sustained graft loss (includes graft failure- defined as the return to long-term dialysis and patient death) within two-years post-transplant. Controls were also selected from the same cohort of included participants and defined as those who had a functioning graft at two-years post-transplant. Matching was performed on analysis time (the time from transplantation to the graft failure or death), gender and presence or absence of diabetes. Matching on age band was attempted; however, it was not possible within the cohort. As recommended, we adjusted for the covariates used in case-control matching in the analysis. [8]

Hospital encounters for maintenance haemodialysis were excluded from the calculation of hospital admission rates. Infection episode was defined as the episode of hospital admission in which any infection was documented during that admission by investigation results or was given an infection-related diagnosis by the treating team. Coronary angiogram results were categorised based on the cardiologists' interpretation provided on the report. An angiogram result was categorised abnormal if the report mentioned the involvement of "any" number of coronary arteries and was reported other than "a minor disease". Remoteness was determined using the postcode of residence in the patient records linked to the postcode concordance available from the Australian Bureau of Statistics (ABS). [9]

Statistical analysis: Analyses were performed using Stata Tx version 15. For the analysis carried out for this study, there were a set of 4 controls per case with matched analysis time, gender and diabetes status. Regression analysis was adjusted for age at renal replacement therapy (RRT) initiation to account for the inability to include matching on age band. Conditional logistic regression was used to generate odds ratio (OR) adjusted for age. For comparison of hospital admission rates, multilevel Poisson regression was used as a paired analysis to account for the random effect of each set of cases and controls. The Incidence rate and incidence rate ratio is presented for the pre-transplant hospital admission rate for the cases and controls. Mean of covariates was compared using pairwise mean comparison, and the OR was calculated using conditional logistic regression. Wilcoxon's signed-rank test and Pearson's $\chi 2$ were used for comparison of baseline characteristics. P-value of <0.05 was considered statistically significant. Data were analysed using Stata 15 statistical software.

Ethical consideration: This study was approved by the Office of Research Ethics, Compliance and Integrity Research Services, The University of Adelaide; Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research; Central Australian Human Research Ethics Committee; Royal Adelaide Hospital- Central Adelaide Local Health Network Human Research Ethics Committee; Flinders Medical Centre- South Adelaide Local Health Network Human Research Ethics Committee; Aboriginal Human Research Ethics Committee, South Australia.

Results:

There were 89 transplant operations among 88 Indigenous kidney transplant recipients who met the inclusion criteria during the study period. There were 17 cases, and 68 matched controls were randomly selected (1:4).

Baseline characteristics:

Table 1 shows the baseline characteristics, including the pre-transplant screening tests of the cases and controls. No difference in the proportion of participants from the SA and NT between the cases and controls was found. No difference was found between the two groups. No difference in the remoteness categories or the presence of comorbidities (reported at the RRT start) was seen between the cases and controls. The OR for remote compared to non-remote was 2.0 (95% CI, 0.7, 6.1). The OR for the comorbidities is presented in Table 2.

Transplant specific information (Table 3):

All of the transplants were from deceased donors. The median age of donor among the cases was higher (52 vs. 45 years). However, the difference was not statistically significant. There was no significant difference in the distribution of HLA mismatch between the cases and controls. Table 4 shows the OR for HLA between cases and the controls.

Pre-transplant hospital admissions:

The hospital admission rate in the two-year pre-transplant period (excluding hospital encounter for maintenance dialysis) was 3.2 per-person years among the cases and 1.6 per-person years among the controls. The overall rate ratio (RR) of pre-transplant hospital admission for cases vs controls was 1.7 (95% CI, 1.3, 2.1). In the

12 months before the transplant, the RR for hospital admission was 1.9 per person-year (95% CI, 1.4, 2.7) for cases vs. controls and 1.4 per person-year (95% CI, 0.9, 1.9) in 13 to 24 months period pre-transplant. No difference in the rate of ICU admission was found between the cases and controls in the two-year pre-transplant period, IRR 1.2 per person (95% CI, 0.2, 5.9). The pre-transplant mean length of stay was similar between the cases and controls 11.9 vs. 8.9 days, respectively.

Admission episodes where an infection was documented:

The rate of admission where infections were documented in the pre-transplant period was 0.6 episodes per-person year among cases and 0.5 episodes per-person year among controls. RR between cases and control for episodes where an infection was documented was 0.9 (95% CI, 0.6, 1.6). Appendix table i shows the type of infection documented during the admissions.

Discussion:

There are persistent disparities in survival after kidney transplantation for Indigenous Australians, [10] with a particular increase in graft loss in the first two years. Infectious diseases related deaths are substantially higher among Indigenous kidney transplant recipients. [11]

Understanding the predictors of these adverse events is critical to improving these outcomes. To evaluate this, we examined cases (all Australian Indigenous kidney transplant recipients from 1st January 2005 to 31 December 2015 from major hospitals in the NT and South Australia (SA) who returned to dialysis or died in the period up to two-years post-transplant). We compared these to controls (matched Indigenous kidney transplant recipients from 1st January 2005 to 31 December 2015 from major hospitals in the NT and SA who had a functioning kidney transplant at two-years post-transplant). This is the first time pre-transplant predictors have been examined in detail among Australian Indigenous transplant recipients. We found that the cases had a higher rate of hospital admission in the two-year pre-transplant period, and an increased frequency of pre-transplant hospital admissions as compared to their matched controls.

We did not find a difference between the cases and controls in other factors; length of hospital stay, remoteness, comorbidities at the start of RRT, pre-transplant screening tests (for infection or cardiovascular disease), pre-transplant cardiovascular intervention, and HLA mismatch.

There is a paucity of data on the effect of pre-transplant morbidities like hospital admission and relationship to kidney transplant outcome. Our findings match the observation made by Lynch et al. [12] They examined the impact of hospitalisation

among waitlisted patients from the United States Renal Data System (and the first year of waitlisting). They reported decreased graft and patient survival among the patients who had higher admissions in the pre-transplant period; however, the survival benefit was preserved among their study participants. In a separate study, Lynch et al. [13] reported that age at RRT initiation, gender, comorbidities except for diabetes, and sensitisation did not predict transplant outcomes. However, hospitalisations in the year before transplantation and length of hospital stay were significantly associated with graft loss and patient death. In contrary to their finding, length of hospital stay was not a predictor of graft loss in our study.

Based on our study findings, we propose that to improve kidney transplant outcomes in the Indigenous Australians, specifically in the first two-year post-transplant, it is essential to act in the pre-transplant period. Efforts to reduce pre-transplant hospital admissions may be helpful. This might include and not be limited to the identification of reasons for admissions and development of strategies to prevent such conditions where possible. Increased hospitalisations in the pre-transplant period could be a reflection of overall higher admission among the Indigenous Australians. [14] Therefore general measures at the community level to improve health among Indigenous Australians may help. Future studies should consider examination of other factors like the effect of severity of comorbidities and dialysis vintage on the transplant outcomes. While better HLA matching could be argued as a logical way to improve graft outcome, in practice, this will cause significant delay for the Indigenous Australians in receiving a kidney transplant. Based on their findings, Molnar et al. developed a post-transplant outcome prediction tool using the data available before the time of transplantation. this tool performed better for ESKD patients in the United States in predicting graft survival than existing prediction tools like Estimated Post-

Transplant Survival score. [15] Consideration may be given to the development of similar tools specific for Australian Indigenous kidney transplant recipients.

Our study is not without limitations. The sample size was small; however, case-control study methodology is statistically robust for identification of factors that may be associated with a rare outcome such as graft loss which involves a latency period for the outcome to occur. The small sample size is intrinsic to the study group and persisted despite the inclusion of all Indigenous transplant recipients during the study period. Optimal matching of cases and controls and using age adjustment in the regression analysis prevented overmatching and introduction of bias. [16] Our cohort included Indigenous Australians with ESKD in South Australia and the Northern Territory; hence the findings may not be generalisable to other jurisdiction in Australia. Finally, due to the nature of data collection, i.e. review of medical records; data for some covariates were missing (e.g. due to absence of discharge summaries, sheets with incomplete details for emergency department encounters and in some cases some volumes of the records were not available for review).

Conclusion:

Our findings suggest that there is an increased rate of pre-transplant hospital admission amongst Indigenous Australians who experience early graft loss. Other factors such as remoteness, comorbidities at the start of RRT, pre-transplant screening tests, and HLA mismatch were not associated with poor outcomes. Efforts to reduce pre-transplant hospital admission rates and the burden of infection may be helpful. Future studies might need to explore other issues specific to ESKD patients, such as the severity of comorbidities, iron stores, phosphate and parathyroid hormone levels, and consideration might be given to the development of outcome prediction tool specific for Indigenous patients. Improvement in record-keeping is also essential to improve the quality of data for studies like ours and thus our ability to understand key predictors for transplant outcomes. Furthermore, broader social determinants of health should be addressed in order to improve pre-transplant health and thus improve both access to transplant and potential for optimal post-transplant outcomes.

Acknowledgements:

The authors acknowledge the support of the renal physicians, renal nurses and administrative staff in the renal and medical records units at each hospital directly or indirectly involved during the data collection. Also, we acknowledge the contribution of the ANZDATA registry, the Indigenous patient representatives and patients. We declare that this research did not receive any specific funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author Contributions:

PL, AC, and SPM participated in conceptualisation, research design, methodology, validation, visualisation, and critical revision of the article. NK participated in data curation, development of methodology, project administration, formal analysis, writing – original draft preparation, and critical revision of article.

Disclosure:

The authors declare no conflicts of interest.

Funding:

The authors did not receive funding support for this research.

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Covariates	Attributes	Controls (n=68)	Cases (n=17)
Residential state	South Australia	20 (39%)	6 (35%)
	Northern Territory	48 (71%)	11 (65%)
Remoteness categories	Remote	28 (41%)	10 (59%)
Age at RRT¶ initiation, median (IQR∞)		42 (33, 48.5)	44 (36, 47)
Ethnicity	Aboriginal	58 (85%)	17 (100%)
	Aboriginal and Torres Strait Islander	10 (15%)	0 (0%)
Coronary artery disease at RRT¶ start	Yes	21 (31%)	1 (6%)
Coronary Angiography	Normal	16 (24%)	5 (29%)
	Minor disease	18 (26%)	2 (12%)
	Abnormal	17 (25%)	5 (29%)
	Not Performed	14 (21%)	2 (12%)
	Missing	3 (4%)	3 (18%)
Pre-transplant Cardiovascular intervention (CABG€ or Angioplasty)	Yes	7 (10%)	2 (12%)
Chronic lung disease at RRT¶ start	Yes	3 (4%)	2 (12%)
Spirometry (Breathing Test)	Abnormal-FEV:FVC¥ 60-69%	7 (10%)	0 (0%)
Cerebrovascular disease at RRT¶ start	Yes	3 (4%)	0 (0%)
Peripheral vascular disease at RRT¶ start	Yes	7 (10%)	3 (18%)
Mantoux Test	LTBI*	31 (46%)	7 (41%)
	Not indicated	33 (49%)	10 (59%)
	Missing	4 (6%)	0 (0%)
Varicella serology	Positive	65 (96%)	16 (94%)
	Missing	0 (0%)	1 (6%)
Cytomegalovirus serology	Positive	68 (100%)	17 (100%)
Epstein-Barr Virus serology	Positive	66 (97%)	16 (94%)
Strongyloides	Equivocal	1 (2%)	0 (0%)
	Positive	8 (18%)	2 (18%)

Treponema Pallidum	Positive	11 (23%)	4 (36%)
Meliod	Positive	4 (13%)	0 (0%)
Toxoplasma	Positive	18 (26%)	3 (18%)
	Not Done	9 (13%)	5 (29%)
Human T-Lymphocytic Virus (HTLV)	Yes	4 (6%)	0 (0%)
Human Immunodeficiency Virus (HIV)	No	68 (100%)	17 (100%)
Hepatitis C	Positive	4 (6%)	1 (6%)
Hepatitis B	Positive	1 (1%)	0 (0%)

Table 1: Baseline characteristics of the cases and controls– showing comorbidities at the renal replacement therapy (RRT) start, and pre-transplant screening test results. ¶ RRT- Renal replacement therapy ∞ IQR- Interquartile range € CABG- Coronary artery bypass graft *LTBI- Latent tuberculosis infection ¥FEV: FVC- Forced expiratory volume: Forced vital capacity ratio

Comorbidities	Odds Ratio (OR), (95%confidence interval, [CI])	P-value
Chronic lung disease	3.4 (0.5, 22.1)	0.2
Coronary artery disease	0.1 (0.0, 1.0)	0.1
Peripheral vascular disease	1.8 (0.4, 7.9)	0.4

Table 2: Odds Ratio for the comorbidities, reported at the renal replacement therapy (RRT) start. Adjusted for age at RRT initiation

Covariates	Attributes	Controls (n=68)	Cases (n=17)
Age at transplant, median (IQR*)		47 (38, 53)	48 (43, 52)
Donor age, median (IQR)		45 (34.5, 58.5)	52 (46, 61)
Donor gender	Female	36 (53%)	11 (65%)
	Male	32 (47%)	6 (35%)
Donor source	Deceased	68 (100%)	17 (100%)
HLA-A¶ mismatch	0	2 (3%)	1 (6%)
	1	23 (34%)	6 (35%)
	2	43 (63%)	10 (59%)
HLA-B¶ mismatch	0	1 (1%)	1 (6%)
	1	13 (19%)	2 (12%)
	2	54 (79%)	14 (82%)
HLA-DR¶ mismatch	0	5 (7%)	1 (6%)
	1	17 (25%)	4 (24%)
	2	46 (68%)	12 (71%)
HLA-DQ¶ mismatch	0	13 (59%)	2 (40%)
	1	8 (36%)	3 (60%)
	2	1 (5%)	0 (0%)

Table 3: Transplant specific information * IQR- Interquartile range ¶ HLA- Human leucocyte antigen

Covariates	Attributes	Odds ratio (OR) for Cases compared to controls (95% Confidence Interval)
Total length of stay	Mean difference between cases and controls 2.9 days (95% CI, -4.7, 10.6)	1 (95% CI, 0.9, 1)
Admission frequency compared to ≤1 episode	> 1 episode	6.2 (95% CI, 1.2- 32.5)
Admission with infection		
IRR¶ of admissions where an infection was documented		0.9 (95% CI, 0.6, 1.6)
HLA-A	compared to two or more mismatch	0.8 (95% CI, 0.3-2.4)
HLA-B	compared to two or more mismatch	1.3 (95% CI, 0.3-5.1)
HLA-DR	compared to two or more mismatch	1.1 (95% CI, 0.3-3.6)

Table 4: Showing Odds ratio (OR) for cases as compared to controls in the pre-transplant period, Adjusted for age at RRT initiation and IRR for admission episode where an infection was documented

*ICU- Intensive care unit, ¶IRR- Incidence rate ratio

Type of infection in the pre-transplant period	Controls	Cases
Bacterial	35 (15.2)	5 (4.6)
Viral	5 (3.0)	7 (6.5)
Others including culture negative	38 (16.5)	10 (9.3)
Not infection	151 (65.4)	86 (79.6)

Appendix 1: Type of infection in the admission episodes where an infection was documented in the 2-year pre-transplant period

CHAPTER 5

Understanding the findings

In this thesis, I sought to identify factors which are associated with access to the waiting list and outcomes of kidney transplantation for Indigenous Australians with ESKD. Our research has added to previous work (14, 75, 83) through utilising updated and recent waiting list information and bringing together hospital derived data with registry information to more comprehensively explore the individual factors associated with the examined outcome measures.

Firstly, the current trend of kidney replacement therapy (KRT) distribution among Indigenous patients with ESKD was explored, and comparisons made to non-indigenous patients. In this study, we confirmed the much higher prevalence of facility-based haemodialysis among Indigenous Australians. (50)

In chapter two, we showed that the likelihood of placement on the transplant waiting list for kidney transplantation was reduced for Indigenous Australians compared to non-indigenous Australians. Also, the time taken to be placed on the waiting list was longer than for their non-indigenous counterparts. (77) "Delays in being accepted for the waiting list consequently lead to patients being near the top of the list at the time of listing, increasing their likelihood of transplantation soon after listing. This is reflected in the shorter median time to transplantation after placement on the transplant waiting list and higher rates of transplantation in the first year after placement on the waiting list, after which the transplantation rate falls." (77) The factors contributing to the remaining gap in accessing waiting list and kidney transplantation among Indigenous Australians with ESKD are yet to be identified and addressed. Some of the factors contributing to the gap could be due to lack of clear understanding of the transplant process and cultural and language barriers as was expressed by those interviewed in the Improving Access to Kidney Transplant

(IMPAKT) project. (10, 97, 98) That study also identified systemic issues as additional barriers affecting access to transplantation.

The process of kidney transplantation has been described as difficult and confusing. The development of a culturally appropriate system that supports Indigenous patients, their families, and clinicians with knowledge of specific cultural needs will be helpful. (100) Participants interviewed in that study demonstrated their interest in receiving a kidney transplant. They demonstrated that their understanding of kidney transplant as the only way to improve quality of life, which allows them to live in the community, unlike dialysis, which requires relocation and makes spending time with family and friends possible. They viewed dialysis as an isolating form of treatment. (100)

The literature, and our study, consistently indicate that remoteness is a key factor in access to the waiting list and kidney transplantation among Indigenous Australians with ESKD. (15, 77, 79, 96, 100-103) The term “remoteness” can be associated with multiple factors that impact access to health care (2) including access to kidney care (e.g. lack of access to specialised services like the pathology services required for a kidney transplant, and the need to travel long distances to be assessed for transplant eligibility to name a few), (15, 71, 79) all of which put people from these areas at a major disadvantage. This emphasises the need for making these services available closer to the remote communities in which patients live.

Despite the use of advanced statistical methods to adjust for the effect of remoteness and other measured factors in our study, the gap in the rates of placement on transplant waiting list between Indigenous and non-indigenous Australians with ESKD was persistent. This highlights the importance of further

qualitative and mixed-method studies to examine patients' perspectives and to understand the factors at the patient level that have a real-world impact on placement on transplant waiting list/transplant opportunities.

The findings from our study, (77) attracted significant media and national attention. Together with observations from other researchers, (15, 89, 100, 101) this led to the establishment of the National Indigenous Kidney Transplantation Taskforce (NIKTT) in 2018. (85) Our study informed the NIKTT's advocacy for equitable access to transplantation for Indigenous Australians with ESKD.

Chapter three examined another specific individual-level factor – attendance at facility haemodialysis. This was examined in an NT-based ESKD cohort. Inability to adhere with the complex medical therapy, particularly with respect to the transplant immunosuppression, is one of the general conditions set out as exclusion criteria for transplantation. (86, 104) Specific guidelines to identify patients at high risk of non-adherence post-transplantation do not exist. Dialysis attendance is often used as a marker of compliance to the medical treatment and is likely to form an important factor in the transplant assessment process at an informal level. (86) A national survey conducted in 2007 raised concerns that the nephrologists' decision to refer or not refer a patient for placement on the transplant waiting list and kidney transplantation was influenced by a patient's adherence to dialysis treatment. (83) We showed a reduced chance of transplantation (placement on the transplant waiting list) among participants with ≤2.5 sessions/week dialysis attendance, and no participants with dialysis attendance in the lowest quintile received a kidney transplant. Nevertheless, there was no association found between dialysis attendance and kidney transplant outcomes.

Although it included all transplants over 16 years, the number of people waitlisted for transplantation was very low—this limited the power of statistical analyses.

Furthermore, our findings highlight the need to understand the reasons behind reduced attendance, which can come from gaining patients' perspectives and review of the health system factors which may be associated with these issues. The relevance of these reasons post-transplantation is not yet known. Frequently, Indigenous patients have voiced the need for availability of dialysis closer to home in the remote community, and dialysis attendance may improve with this change. (79) Given that, the remote Australian communities are widely distributed over a big landmass, the development of sustainable infrastructure is extremely difficult. When the number of people accessing the waiting list and receiving a kidney transplant increases, the effect of dialysis attendance on kidney transplant outcomes may be explored again. Mixed-method studies and examination of recent data might allow further understanding of other factors that affect attendance, placement on the transplant waiting list and transplantation.

Finally, two projects (described in chapter 4.1 and 4.2) were designed to identify factors associated with graft loss (including patient death). Both studies were conducted in the cohort of Indigenous kidney transplant recipients from 2005 to 2015.

The descriptive cohort study (described in chapter 4.1, pages 84-111) identified the morbidity burden among Indigenous kidney transplant recipients in the pre- and post-transplant period. We found that there was an increased burden of hospitalisation in the post-transplant period. This burden was higher in the first year post-transplantation. Based on our findings (described in chapter 4.1, pages 84-111),

development of evidence-based management protocols to help reduce the rates of hospitalisation, infections, length of inpatient stay, and the severity of illness during these episodes should be considered and focused on issues in the first-year post-transplantation. Because rates of infection in the post-transplant hospital admission were higher in our study population, we suggest that consideration should be given to modification of existing anti-infective prophylaxis (e.g. lengthen the duration of antiviral prophylaxis) protocols in the post-transplant period.

Fifty per cent of our study population suffered from delayed graft function (DGF), and 55% of the study population had a total ischaemia time of >16 hours. DGF is associated with poor graft outcomes, [105] and reduction in cold ischaemia time is associated with a lower incidence of DGF. (15, 106) Measures to reduce the cold ischaemia time by addressing issues associated with the transfer of participants to the transplanting centres may be useful in reducing the frequency of such adverse events in our study population. It is important to note that almost 50% of our study population were residents of the NT. The NT ESKD patients undergo kidney transplants in South Australia (SA) and must fly to the transplanting hospital upon acceptance of the organ offered. For a potential recipient who resides in the remote and very remote areas of the NT, it takes several hours to access the nearest airport leading to significant time lag to reach the transplanting hospital in SA. New methods of organ preservation may reduce the impact of long cold ischaemia time and hence reduce one of the hurdles associated with remoteness.

Furthermore, community-level efforts to reduce overall infection and hospital admission rates among Indigenous Australians may also be important.

In the study described in chapter 4.2 (pages 114-137), a retrospective comparison of cases with matched controls (1:4) selected from an above cohort of Indigenous transplant recipients (included in the study described in chapter 4.1), was performed. Besides increased rates of hospitalisation in the pre-transplant period, other factors examined (length of hospital stay, remoteness, comorbidities at the start of KRT, pre-transplant screening tests (for infection or cardiovascular disease), pre-transplant cardiovascular intervention, and HLA mismatch) did not show a causal relationship with graft loss within the two-year post-transplant period. While this is not an uncommon finding in other parts of the world, (107, 108) this is the first time such an observation has been made among Indigenous Australian kidney transplant recipients. The reasons for increased hospitalisation may be specific to ESKD or more general issues which drive hospitalisation rates of non-dialysis Indigenous Australians from remote areas. (2)

Other areas for further investigation include identification of reasons for admissions and development of strategies to prevent such conditions where possible to reduce pre-transplant hospital admissions.

Conclusion

Our study confirmed the high prevalence of facility-based haemodialysis among Indigenous Australians with ESKD. This high prevalence translates into potential barriers to regular attendance and utilisation of dialysis services and possibly a need for relocation to improve access to kidney care. While alternative treatments at home are possible, there are significant challenges to make this a sustainable solution. In such circumstances, kidney transplant appears a suitable option to enable Indigenous Australians to receive treatment closer to their home and community. However, we found that Indigenous Australians with ESKD had significantly lower chances of placement on the transplant waiting list and transplantation. Existing research and our study suggest that understanding the multitude of factors associated with health and patterns of health service utilisation in remote communities might provide a broader knowledge base to better assist healthcare providers in making decisions that impact Indigenous patient care.

The critical findings of our study show that less than 2% of Indigenous patients in our cohort receiving KRT were waitlisted for a deceased donor kidney transplant. Our study found no correlation between dialysis attendance and transplant outcomes, although this is a factor that influences nephrologists' decisions to refer patients for transplant assessment and transplantation. Raising awareness and initiation/ reinforcement of education when one is at a relatively earlier stage of CKD may help. Measures to perform most of the transplant workup closer to the dialysis unit, and hence closer to a patient's home, might reduce the need for recurrent travel and may improve attendance at transplant centres for the pre-transplant tests which cannot be performed elsewhere. Utilisation of existing Indigenous transplant recipients in the transplant education seminars to share their journey with participants on dialysis may

also be helpful by reducing the communication gap when using the non-indigenous educators. Supporting the development of consumer representative groups to be the voice of these patients, and ensuring consumer consultation in the development of management protocols should be considered.

Additionally, we showed the need for better understanding of the reasons for frequent hospitalisation. Strategies to prevent widespread infection (including reinforcement of hygiene measures, newer solutions for over-crowding) and programs from raising infection awareness may be helpful. Measures to reduce delayed graft function by reduction of cold ischaemia time may also be helpful. Development of better immunosuppression protocols taking into consideration pharmacokinetic and pharmacodynamic differences, tailored to Indigenous transplant patients, may help reduce some of the infections in the post-transplant period.

One of the key steps in transplantation is the final step of organ allocation to the potential patient on the transplant waiting list. Organ allocation is based on following criteria set out by Transplant Society of Australia and New Zealand: Blood group compatible (e.g. A to A) and blood group acceptable (e.g. O to B); waiting time; HLA matching (tissue typing to determine the level of immunological compatibility between a donor and recipient); HLA-antibody detection (which can identify unacceptable HLA antigens, and be used to preclude certain donors); certain priority allocations (e.g. paediatric recipients defined as age <18 years, combined organ recipients such as kidney-pancreas, highly sensitised recipients); and the requirement to maintain an equitable flow of kidneys between states and territories. This algorithm is set to balance parity across transplant jurisdictions, equity and standardisation of the allocation process. (104) Remote location of patients do not

demerit their chance of transplantation. Whether remoteness impacts patients' decision to receive a marginal kidney or their nephrologists' decision to accept such a kidney is unknown. Also, whether a change in the current allocation process to eplets matching be beneficial for Indigenous Australians with ESKD remains unclear- an aspect that deserves further exploration. Despite an extensive search, the data on when and whether the transplant recipients were able to return to their community post-transplant was incomplete in our study. Improved record keeping will help outline the journey of the transplant recipients and help identify other barriers to be overcome.

Furthermore, we found that the only factor in the pre-transplant period, which predicted early graft-loss among Indigenous transplant recipients was increased rates of pre-transplant hospitalisation. A better understanding of the underlying reasons for hospitalisations among Indigenous Australians with ESKD, and measures to reduce these events, should be prioritised. Finally, more studies to identify other factors which play a role in determining access to the waiting list, kidney transplantation and improving transplant outcomes among Indigenous Australians with ESKD are needed.

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