ORIGINAL ARTICLE

Allograft outcome following repeat transplantation of patients with non-adherence-related first kidney allograft failure: a population cohort study

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SUMMARY

Nonadherence is an important risk factor for premature allograft failure after kidney transplantation, but outcomes after re-transplantation remain uncertain. Using data from the Australian and New Zealand Dialysis and Transplant registry, the associations between causes of first allograft failure and acute rejection-related and non-adherence-related allograft failure following re-transplantation were examined using competing risk analyses, treating the respective alternative causes of allograft failure and death with functioning graft as competing events. Fifty-nine of 2450 patients (2%) lost their first allografts from nonadherence. Patients who lost their first kidney allograft from nonadherence were younger at the time of first kidney allograft failure but waited longer for a second allograft (>5 years: 54% vs. 20%, $P < 0.001$) compared with other causes. Compared with patients who lost their first allograft from causes other than nonadherence, the adjusted subdistribution hazard ratio (HR and 95% CI) for acute rejection-related second allograft failure was 0.58 (0.08, 4.07; $P = 0.582$) for patients with allograft failure attributed to nonadherence and was 6.30 (1.34, 29.67; $P = 0.020$) for non-adherence-related second allograft failure. In this cohort of transplant recipients who have received second allografts, first allograft failure secondary to nonadherence was associated with a marginally greater risk of allograft failure attributed to nonadherence in subsequent transplantation.

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Key words
allograft survival, kidney transplantation, nonadherence, registry

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Introduction

Nonadherence to immunosuppressive medications is common after kidney transplantation [1,2]. While nonadherence is a significant issue in all solid organ transplants, rates of immunosuppressant nonadherence may be highest among kidney transplant recipients [3]. The overall prevalence rate of nonadherence is estimated to be between 30% and 50%, although the true incidence is likely to vary according to the characteristics of the patient population [4]. Prior research has reported that young adulthood, particularly during the transition phase from pediatric to adult care, poses the greatest risk of medication nonadherence [5]. The clinical and economic consequences of nonadherence are substantial. Nonadherence is a major risk factor for *de novo* donor-specific anti-human leukocyte antigen (HLA) antibodies, acute and chronic rejection, with the risk of renal allograft failure estimated at up to 7-times greater in patients who were nonadherent compared with adherent patients [6,7]. In the United States, nonadherence to immunosuppressive medications is estimated to cost up to USD$100 million annually, through increased rates of hospitalization, costs related to the re-initiation of dialysis and re-transplantation following premature allograft failure [8].

Repeat kidney transplantation for patients who have lost their first kidney allograft from nonadherence presents a clinical dilemma for transplant clinicians. The decisional conflict of maximizing survival gains from re-transplantation and the risk of repeat nonadherence culminating in acute rejection and premature allograft failure among clinicians and healthcare professionals is paramount. The ethical context of the arguments for and against the eligibility for repeat transplantation becomes an important focus as the alternative of lifelong dialysis treatment is deemed unacceptable [4,9]. In the context of competing options, robust data and knowledge are needed to inform the next course of action. There is a lack of data concerning the allograft outcome following re-transplantation of patients who have experienced prior allograft failure from nonadherence, with findings from a single center study showing comparable allograft survival between patients with and without a prior history of nonadherence [10,11]. A greater understanding of the outcome following re-transplantation in patients who have experienced allograft failure from nonadherence will assist clinicians and patients in the decision-making process when considering re-transplantation. The aim of this study was to evaluate the risk of nonadherence and acute rejection-related second allograft failure in patients who have lost their first kidney allograft from nonadherence compared with other causes.

Materials and methods

Study population

Patients with end-stage kidney disease who have received a second live or deceased donor kidney allograft since the inception of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) registry in 1977 were included, with follow-up until December 2014. All transplants occurred in the 24 accredited transplanting centers [8 pediatric (up to age 16 years) and 16 adult transplanting centers] in Australia and New Zealand. Patients located at sites with no expertise in kidney transplantation were referred for assessment and transplantation at these sites. Recipients of multiple organ allografts were excluded. Informed consent was not required because only de-identified data were utilized for analysis. However, consent for inclusion in the ANZDATA registry is sought from all patients with end-stage kidney disease (ESKD) in Australia and New Zealand. The clinical and research activities being reported are consistent with the Principles of the *Declaration of Istanbul* as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism".

Exposure

Patients were categorized into two groups according to whether the cause of their first allograft failure was attributed to nonadherence (i.e., first allograft failure secondary to nonadherence) or other causes such as chronic allograft nephropathy/interstitial fibrosis and tubular atrophy (CAN/IFTA), acute rejection, recurrent or *de novo* glomerulonephritis, vascular/technical complications, and other miscellaneous causes as recorded in the ANZDATA registry survey form (i.e., first allograft failure from other causes). Clinicians defined nonadherence where the cause of allograft failure was attributable to noncompliance with immunosuppressive therapy. However, ANZDATA registry does not verify the accuracy of this diagnosis.

Data collection

Baseline characteristics included recipient factors of age, gender, ethnicity, body mass index (BMI), waiting time prior to transplantation, comorbid conditions

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(including diabetes status and coronary artery disease), smoking history, and primary cause of ESKD; donor age, gender, and type; immunological characteristics of peak percentage panel reactive antibody (%PRA) and number of HLA-mismatches; and transplant-related factors such as total ischemic time, use of induction therapy, initial immunosuppression (calcineurin-inhibitor, anti-metabolite and prednisolone), and transplant year. Donor and recipient age, donor type, waiting time, and immunological characteristics were extracted for both first and second kidney allografts.

Clinical outcomes

The primary clinical outcome was functional allograft failure (death with a functioning graft was either censored or considered as a competing event) following second transplant. Secondary outcomes included overall allograft failure following second transplant (including allograft failure and death with a functioning graft), second allograft failure attributed to nonadherence, second allograft failure attributed to acute rejection, and acute rejection in the first 6 months post-second transplant. Acute rejection episodes within 6 months post-transplant were reported to the ANZDATA registry from 1997, and therefore analysis for acute rejection was restricted to the study cohort who had received a second kidney allograft between 1997 and 2014. Types of acute rejection (i.e., cellular, vascular, or glomerular) were also reported to the ANZDATA registry, although acute humoral rejection was only reported from 2005.

Statistical analyses

Baseline characteristics were expressed as number (proportion), median [interquartile range (IQR)], and mean (standard deviation, SD) where appropriate; with comparisons between exposure groups examined using chi-square test, Kruskal–Wallis test and one-way analysis of variance, respectively. The associations between causes of first allograft failure (nonadherence versus other causes), functional allograft failure (death with a functioning graft was censored), overall allograft failure and acute rejection at 6 months after second transplants were examined using multivariable Cox proportional hazards regression analyses. The proportional hazards assumptions of all Cox regression models were checked graphically by plotting the Schoenfeld residuals, with no evidence of departures from proportional hazards.

Competing risk regression analyses using the method of Fine and Gray [12] were undertaken for different causes of allograft failure (i.e., nonadherence and acute rejection-related allograft failure) after second kidney transplants, treating the respective alternative cause of allograft failure and death with functioning graft as competing events. For second functional allograft failure, the competing event was death with a functioning graft. For non-adherence-related second allograft failure, the competing events were allograft failure attributed to causes other than nonadherence (i.e., CAN/IFTA, acute rejection, glomerulonephritis, vascular complications, and other miscellaneous causes) and death with a functioning graft. For rejection-related second allograft failure, the competing events were allograft failure attributed to causes other than rejection (i.e., CAN/IFTA, nonadherence, glomerulonephritis, vascular complications, and other miscellaneous causes) and death with a functioning graft.

Covariates associated with each clinical outcome with P-values of <0.05 in the unadjusted analyses were included in the multivariable-adjusted Cox regression and competing risk analyses, with results expressed as hazard ratio (HR) or subdistribution HR with 95% confidence interval (95% CI), respectively. However, donor and recipient age, ethnicity, era, HLA-mismatches, and waiting time were included in all models given their biological relationships with allograft outcomes. Two-way interactions between causes of first allograft failure and era was examined for all clinical outcomes. All analyses were undertaken using SPSS V10 statistical software program (SPSS Inc., North Sydney, NSW, Australia) and STATA (version 11 StataCorp LP, College Station, TX, USA).

Results

Study population

Of 2822 patients who had received a second kidney allograft, 372 were excluded because there were no records of the causes and/or dates of first allograft failure leaving a study cohort of 2450 patients. Of these, 59 (2.4%) lost their first kidney allograft because of nonadherence. Baseline characteristics of the study population according to the cause of first kidney allograft failure (nonadherence versus other causes) are shown in Table 1. The median (IQR) allograft follow-up time for patients with first kidney allograft failure secondary to nonadherence [4.3 (2.4–8.3) years] was similar to those with first kidney allograft failure from other causes [5.6 (1.6–11.6) years; $P = 0.47$]. Similar median patient follow-up time was observed between the two groups. Of

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Table 1. Baseline characteristics of patients who have received a second renal allograft stratified by causes of first allograft failure (n = 2450).

	Nonadherence (n = 59)	Other causes (n = 2391)	P-value
Demographics			
Age [years, median (IQR)]			
First allograft	19 (14–23)	29 (20–40)	<0.001
First allograft loss	23 (19–29)	36 (25–45)	<0.001
Second allograft	33 (25–38)	41 (30–51)	<0.001
Male (n, %)	38 (64.4)	1445 (60.4)	0.537
Ethnicity (n, %)			
Caucasian	48 (81.4)	2128 (89.0)	0.012
Indigenous	7 (11.9)	96 (4.0)	
Others	4 (6.7)	167 (7.0)	
Coronary artery disease (n, %)	0 (0.0)	115 (4.8)	0.058
Diabetes (n, %)	0 (0.0)	95 (4.0)	0.094
Body mass index [kg/m^2, median (IQR)]			
First allograft	21.4 (18.6–25.5)	22.6 (19.9–25.9)	0.117
Second allograft	21.2 (18.2–25.5)	22.3 (19.4–25.8)	0.395
Waiting time			
First allograft			
0–1 years	30 (50.9)	1072 (44.8)	0.600
>1–3 years	17 (28.8)	795 (33.2)	
>3–5 years	7 (11.9)	193 (8.1)	
>5 years	2 (3.3)	114 (4.8)	
Unknown	3 (5.1)	217 (9.1)	<0.001
Second allograft			
0–1 years	3 (5.1)	601 (25.1)	
>1–3 years	14 (23.7)	878 (36.8)	
>3–5 years	10 (16.9)	438 (18.3)	
>5 years	32 (54.2)	474 (19.8)	
Smoker (n, %)			
Nonsmoker	31 (52.6)	1056 44.2)	<0.001
Former smoker	12 (20.3)	324 (13.6)	
Current smoker	11 (18.6)	201 (8.4)	
Unknown status	5 (8.5)	810 (33.9)	
Causes of ESKD (n, %)			
Glomerulonephritis (GN)	20 (33.9)	1101 (46.0)	0.016
Diabetes	0 (0.0)	75 (3.1)	
Cystic diseases	2 (3.4)	173 (7.3)	
Vascular	1 (1.7)	43 (1.8)	
Reflux nephropathy	17 (28.8)	357 (14.9)	
Others	19 (32.2)	642 (26.9)	
Causes of first allograft loss (n, %)			
CAN/IFTA	0 (0.0)	1389 (58.1)	<0.001
Acute rejection	0 (0.0)	457 (19.1)	
Recurrent/*de novo* glomerulonephritis	0 (0.0)	168 (7.0)	
Vascular complications	0 (0.0)	206 (8.6)	
Nonadherence	59 (100.0)	0 (0.0)	
Others/missing information	0 (0.0)	171 (7.2)	
Survival of first allograft in years (median [IQR])	5.8 (3.4–10.1)	4.1 (0.2–10.2)	<0.001
Peak PRA			
First allograft			
0–10%	44 (74.6)	1507 (63.0)	0.349
11–50%	9 (15.3)	393 (16.4)	
51–75%	1 (1.7)	104 (4.3)	
>75%	2 (3.3)	121 (5.1)	
Not recorded	3 (5.1)	266 (11.2)	

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Table 1. Continued.

	Nonadherence (*n* = 59)	Other causes (*n* = 2391)	*P*-value
Second allograft			
0–10%	17 (28.8)	766 (32.0)	0.909
11–50%	20 (33.9)	706 (29.5)	
51–75%	8 (13.6)	313 (13.1)	
>75%	14 (23.7)	539 (22.6)	
Not recorded	0 (0.0)	67 (2.8)	
Donor characteristics			
Age [years, median (IQR)]			
First allograft	38 (26–46)	38 (22–49)	0.654
Second allograft	42 (28–53)	40 (24–52)	0.306
Type (*n*, %)			
Live donor (first allograft)	30 (53.6)	561 (23.5)	0.001
Live donor (second allograft)	17 (28.8)	522 (21.8)	0.201
ABO-incompatible (second allograft)	4 (6.8)	31 (1.3)	<0.001
Immunology/transplant			
HLA-ABDR mismatches (median [IQR])			
First allograft	2 (1–3)	3 (2–4)	0.012
Second allograft	3 (2–4)	3 (2–4)	0.233
Ischemic time (h, median [IQR])			
First allograft	3 (1–17)	13 (2–20)	0.008
Second allograft	12 (4–17)	12 (5–17)	0.669
Transplant era: second allograft (*n*, %)			
1980–1988	4 (6.8)	550 (23.0)	<0.001
1989–1997	4 (6.8)	556 (23.3)	
1998–2006	18 (30.5)	582 (24.3)	
2007–2014	33 (55.9)	703 (29.4)	
Initial immunosuppression—second allograft (*n*, %)			
Prednisolone (yes)	57 (96.6)	2205 (92.2)	0.211
Calcineurin-inhibitor			
Cyclosporin	15 (25.4)	1095 (45.8)	<0.001
Tacrolimus	43 (72.9)	883 (36.9)	
Unknown/missing	1 (1.7)	413 (17.3)	
Anti-metabolite			
MMF	52 (88.1)	1231 (51.4)	<0.001
Azathioprine	6 (10.2)	882 (36.9)	
Unknown/missing	1 (1.7)	278 (11.7)	

ESKD, end-stage kidney disease; GN, glomerulonephritis; HLA, human leukocyte antigen; PRA, panel reactive antibody.
Data expressed as number (proportion) or as median (interquartile range [IQR]).

the 59 patients with first allograft failure attributed to nonadherence, the proportion of patients who were retransplanted increased in successive eras (1980–1988: 0.7%; 1989–1997: 0.7%; 1998–2006: 3.0%; 2007–2014: 4.5%). A greater proportion of recipients who had lost their first allografts from nonadherence received tacrolimus and mycophenolate as initial immunosuppressive agents during their second allograft, compared with those who had lost their first allograft from other causes.

The median (IQR, range) age at time of second transplant was 41 (30–50; range 2–73) years; whereas the median (IQR, range) age at time of first transplant was 29 (20–40; range 1–64) years. Patients who lost their first kidney allograft from nonadherence were younger at the time of first kidney allograft [median (IQR) 19 (14–23) vs. 29 (20–40); $P < 0.001$], at the time of first kidney allograft failure [median (IQR) 23 (19–29) vs. 36 (25–45); $P < 0.001$] and at the time of second kidney allograft [median (IQR) 33 (25–38) vs. 41 (30–51); $P < 0.001$] compared with those who lost their first allograft from other causes. Median duration of first kidney allograft survival (5.8 vs. 4.1 years, $P < 0.001$) and waiting time prior to second kidney transplant (waiting time

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>5 years: 54% vs. 20%, $P < 0.001$) were longer in patients who had lost their first kidney allograft from nonadherence compared with other causes. In the cohort of 59 recipients who had received a second kidney allograft after losing the first allograft from nonadherence, the median (IQR) time between first allograft failure and second kidney allograft was 5.2 (2.3–5.2) years. Of patients with first allograft failure attributed to nonadherence, deceased and live donors accounted for 71% and 29% of second kidney transplants, respectively. Of the 17 patients who have received a second kidney transplant from live donors, 6 (35%) were from parental donors and 6 (35%) were sibling donors. In contrast, of patients with first allograft failure from causes other than nonadherence, deceased and live donors accounted for 78% and 22% of second kidney transplants, respectively. The proportion of highly sensitized patients substantially increased between first and second kidney transplants in both patient groups who had lost their first kidney allograft from nonadherence and from other causes (peak PRA >75% prior to first allograft: 3% vs. 5%; peak PRA >75% prior to second allograft: 24% vs. 23%). Of patients who lost their first kidney allograft from causes other than nonadherence, CAN/IFTA, acute rejection, and recurrent/*de novo* glomerulonephritis were responsible for 51%, 15%, and 6% of first allograft failures, respectively.

Causes of functional allograft failure in second allografts

A total of 942 patients lost their second allografts during the follow-up period, with non-adherence-related second allograft failure occurred in 11 [of 362 (3.0%)] and 7 [of 580 (1.2%)] patients aged ≤30 years and >30 years at time of second allografts, respectively ($P = 0.026$). CAN/IFTA was the predominant cause of second allograft failure in over 50% of patients. Nonadherence was the cause of second allograft failure in 3 (18%) and 15 (2%) patients who had lost their first kidney allograft from nonadherence and from other causes, respectively; whereas acute rejection was the cause in 18% and 25%, respectively (Fig. 1).

Association between causes of first allograft failure and risk of second functional allograft failure

In a Cox regression analysis censoring for death with a functioning graft, the adjusted HR for second functional allograft failure for those who had lost their first allograft from nonadherence was 0.98 (95% CI 0.58, 1.66; $P = 0.95$), compared with those with first allograft failure from other causes. Other covariates associated with second functional allograft failure are shown in Table 2. There was no significant interaction between causes of first allograft failure and transplant era for functional allograft failure following second allograft (P-value for interaction 0.32).

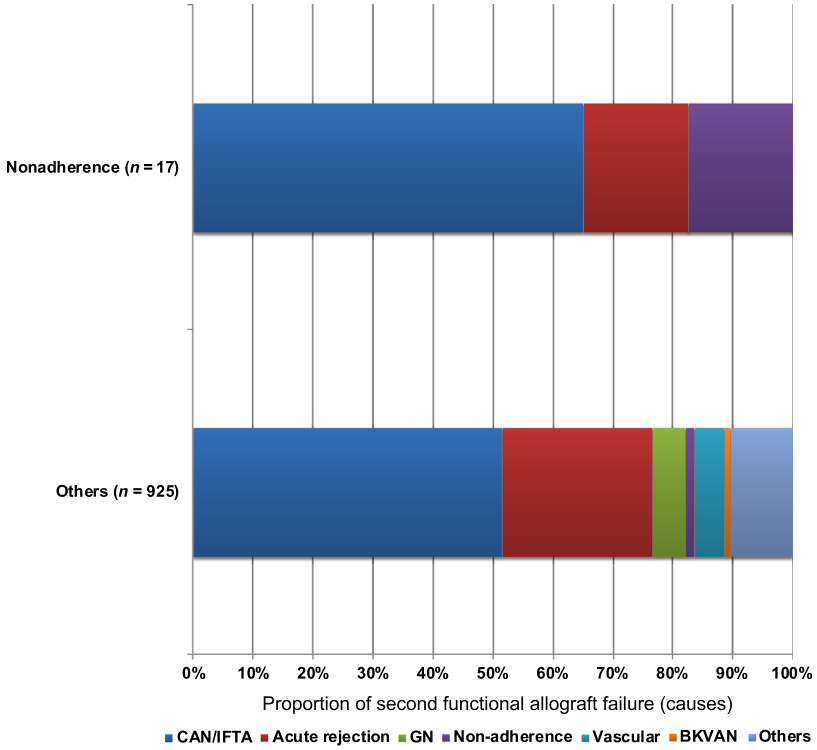

Figure 1 Causes of functional allograft failure following second kidney transplantation, by recipients with first allograft failure attributed to non-adherence or from other causes. BKVAN, BK viral allograft nephropathy; CAN/IFTA, chronic allograft nephropathy/interstitial fibrosis and tubular atrophy; GN, glomerulonephritis.

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Table 2. Associations between causes of first allograft failure and outcomes following second kidney transplant.

	Second functional allograft failure Adjusted HR (95% CI)	Non-adherence-related second allograft failure Subdistribution adjusted HR (95% CI)	Acute rejection-related second allograft failure Subdistribution adjusted HR (95% CI)
Causes of first allograft loss			
Other causes	1.00	1.00	1.00
Nonadherence	0.98 (0.58, 1.66)	6.30 (1.34, 29.67)	0.58 (0.08, 4.07)
Recipient age (per year increase)	0.98 (0.98, 0.99)	0.93 (0.89, 0.97)	1.00 (0.99, 1.01)
Donor age (per year increase)	1.02 (1.01, 1.02)	1.00 (0.98, 1.02)	1.02 (1.00, 1.03)
Race			
Caucasian	1.00	1.00	1.00
Indigenous	1.65 (1.17, 2.31)	3.33 (0.82, 13.47)	0.99 (0.40, 2.43)
Others	0.99 (0.71, 1.37)	2.15 (0.47, 9.92)	1.04 (0.49, 2.20)
Duration of first allograft (per year increase)	0.96 (0.95, 0.98)	–	0.85 (0.80, 0.91)
Dialysis duration prior to second allograft (per year increase)	1.02 (0.99, 1.05)	–	–
HLA-ABDR mismatches	1.12 (1.07, 1.19)	0.85 (0.62, 1.84)	1.21 (1.07, 1.37)
Total ischemic time (per hour increase)	1.02 (1.00, 1.04)	–	1.01 (0.97, 1.07)
Peak PRA			
0–10%	1.00	1.00	1.00
11–50%	1.37 (1.12, 1.69)	1.85 (0.61, 5.65)	1.41 (0.82, 2.41)
51–75%	1.41 (1.09, 1.82)	0.47 (0.05, 4.05)	1.07 (0.54, 2.10)
>75%	1.51 (1.20, 1.90)	0.66 (0.16, 2.77)	2.24 (1.35, 3.72)
Transplant era (2nd allograft)			
1980–1988	1.00	1.00	1.00
1989–1997	0.89 (0.71, 1.12)	1.38 (0.37, 5.18)	0.59 (0.34, 1.00)
1998–2006	0.74 (0.57, 0.98)	1.16 (0.27, 5.01)	0.25 (0.13, 0.51)
2007–2014	0.51 (0.35, 0.73)	2.28 (0.47, 11.10)	0.26 (0.80, 0.91)

HLA, human leukocyte antigen; PRA, panel reactive antibody.

Data presented as adjusted hazard ratios (HR) or subdistribution HR [with 95% confidence intervals (95% CI)] from Cox regression (for second functional allograft failure where death with a functioning graft was censored) and competing risk models (for non-adherence-related and acute rejection-related allograft failure where the respective alternative cause of allograft failure and death with functioning graft were considered as competing events), respectively.

In the competing risk analysis where death with a functioning graft was considered as a competing event, the adjusted subdistribution HR for second functional allograft failure for those who had lost their first allograft from nonadherence was 0.97 (95% CI 0.58, 1.62; $P = 0.910$), compared with those with first allograft failure from other causes. The cumulative incidence curves of second functional allograft failure, stratified by causes of first allograft failure (nonadherence versus other causes), adjusted for the competing risk of death with a functioning graft is shown in Fig. 2.

Association between causes of first allograft failure and risk of second overall allograft failure

In both the unadjusted and adjusted models, there were no associations between the causes of first allograft failure and risk of overall allograft failure after second kidney allografts. The adjusted HR for overall allograft failure was 0.89 (95% CI 0.55, 1.46; $P = 0.659$) in patients with first allograft failure attributed to nonadherence compared with those with first allograft failure because of other causes.

Association between causes of first allograft failure and risk of cause-specific second allograft failure

In the competing risk analysis where death with a functioning graft and second allograft failure attributed to causes other than nonadherence were considered as competing events, the subdistribution HR for non-adherence-related second allograft failure was 6.30 (95% CI 1.34, 29.67; $P = 0.020$) for patients who had lost their first allograft from nonadherence, compared with those with first allograft failure from other causes. Figure 3 shows the cumulative incidence curves of non-

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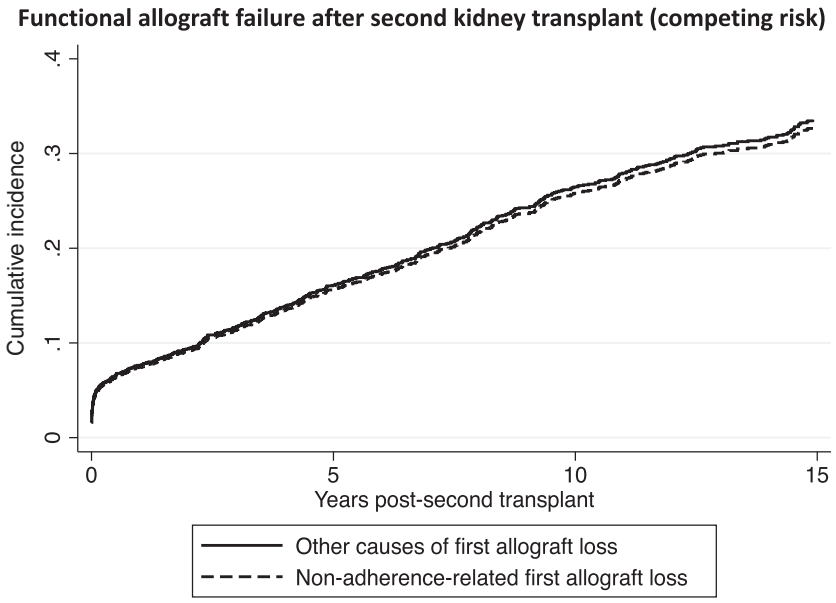

Figure 2 Adjusted cumulative incidence of functional allograft failure, stratified by causes of first allograft failure (non-adherence versus other causes), adjusted for the competing risk of death with a functioning graft.

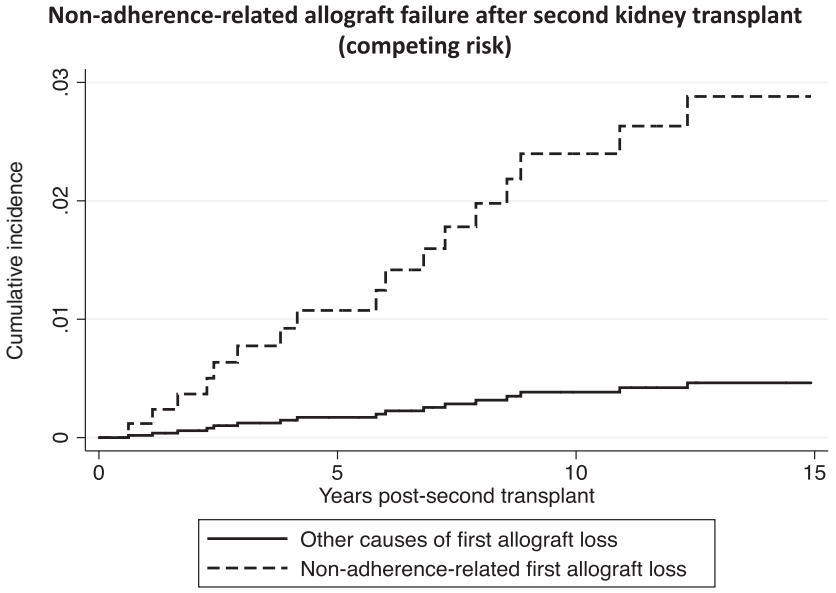

Figure 3 Adjusted cumulative incidence of non-adherence-related second allograft failure, stratified by causes of first allograft failure (non-adherence versus other causes), adjusted for the competing risk of causes of second allograft failure other than non-adherence and death with a functioning graft.

adherence-related second allograft failure, stratified by causes of first allograft failure, adjusted for the competing risk of death with a functioning graft and second allograft failure attributed to causes other than nonadherence.

In the competing risk analysis where death with a functioning graft and second allograft failure attributed to causes other than acute rejection were considered as competing events, the subdistribution HR for rejection-related second allograft failure was 0.58 (95% CI 0.08, 4.07; $P = 0.582$) for patients who had lost their first allograft from nonadherence, compared with those with first allograft failure from other causes (Table 2).

Association between causes of first allograft failure and risk of acute rejection in the second allograft

In the analysis restricted to patients who had received their second allograft between 1997 and 2014 ($n = 1397$ of 2822, 57% of study cohort), there was no association between causes of first allograft failure and acute rejection within the first 6 months after second kidney transplant. The adjusted HR for acute rejection within 6 months for those who had lost their first allograft from nonadherence was 0.95 (95% CI 0.57, 1.59; $P = 0.844$), compared with those with first allograft failure from other causes.

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The median (IQR) time to first acute rejection (of second allograft) for patients who lost their first allograft from nonadherence was 14 (7–58) days, compared with 10 (6–26) days in patients with allograft failure from other causes ($P = 0.22$; Table 3). The incidence and types of first acute rejection episodes were not significantly different between both groups (Table 3).

Discussion

In this longitudinal cohort of patients who have received second kidney allografts, first allograft failure secondary to nonadherence was not associated with a statistically increased risk of functional allograft failure, overall allograft failure or acute rejection following re-transplantation. However, an increased risk of second allograft failure attributed to nonadherence was observed in those who lost their first allografts from nonadherence. However, given the small number of patients who had lost their second allografts because of nonadherence and wide confidence intervals of the estimate, the association between prior non-adherence-related allograft failure and risk of second allograft failure from nonadherence remains uncertain.

The association between first allograft failure secondary to nonadherence and outcome following repeat transplantation remains poorly described, largely limited to two reports from one center in the US [10,11]. In the larger of the cohorts comprising of 5098 kidney transplant recipients between 1982 and 2006, 119 (2%) patients lost their first allograft from overt nonadherence, with 38 (32%) of these patients re-transplanted. Patients who were re-transplanted following prior nonadherence were significantly younger at time of first transplant compared with those who lost their allografts from other causes. After 8-year follow-up post-second kidney transplant, there was no significant difference in death censored allograft failure between patients who lost their prior allograft from nonadherence compared with other causes [11].

Similarly, our study has shown that patients who lost their first allograft from nonadherence were younger, with a similar proportion re-transplanted. It is interesting to note that the median age of first allograft failure from nonadherence is approximately 20 years, reflecting the increasing recognition of the "at risk" status of young adults and those in transition from pediatric/adolescent to adult transplant services. It has been suggested that once past adolescence, nonadherence could be considered stable over the life course, until individuals are affected by cognitive, sensory, and functional impairment associated with older age [4]. The risks of overall and functional allograft failure after re-transplantation were not different between groups, although a greater proportion of patients who had lost their first allograft from nonadherence had also lost their second allograft from nonadherence, compared with those who had experienced first allograft failure from causes other than nonadherence. Time and life experience are likely to have modified the behavior patterns of patients who had lost their first allograft from nonadherence, which may have led to positive adjustments to their healthcare needs. A greater proportion of recipients who had lost their first allografts secondary to nonadherence had received live-donor allografts (for the first transplant), although the proportion of live-donor transplants for

Table 3. Comparisons of the incidences, timing and types of first acute rejection episodes between patients with second allografts according to causes of first allograft failure (nonadherence versus other causes).

	Non-adherence-related first allograft failure	Other causes of first allograft failure	*P*-value
Rejection occurring in the first 6 months			
Incidence	16/52 (30.8%)	385/1345 (28.6%)	0.74
Median time to rejection (days)*	13.5 (7.0–57.5)	10.0 (6.0–26.0)	0.22
Types of first rejection in first 6 months*			
Cellular	75%	65%	0.42
Vascular	0%	9%	0.21
Glomerular	19%	31%	0.31
Humoral†	25%	39%	0.29

Data restricted to the cohort of patients who had received a second allograft between 1997 and 2014.

*Analysis restricted to patients who had experienced acute rejection within the first 6 months post-transplant.

†Restricted to the era between 2005 and 2014.

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second allografts was similar between the two groups (29% of recipients who had lost their first allograft from nonadherence vs. 22% from other causes). Attaining a live-donor transplant may bypass or shorten the duration of dialysis, and hence avoid the symptoms of uremia, time commitment of dialysis treatment, and associated complications. It may be that these differences in life experiences are contributing factors to the development of nonadherent behaviors. Conversely, experience, maturity, and growing responsibilities such as family and employment may have negated this unfavorable behavior. It is notable that a greater proportion of patients with non-adherence-related first allograft failure waited significantly longer prior to repeat transplantation compared with those who lost their first allografts from other causes. This may suggest clinician's reluctance to consider early repeat transplantation in those with non-adherence-related allograft failure.

Nonadherence has been shown to be an independent risk factor for acute rejection, particularly antibody-mediated rejection and late rejection, both of which are strongly associated with premature allograft failure [13–17]. The association between nonadherence and rejection following repeat transplantation remains inconsistent. In the small study by Dunn *et al*. [11], the authors found that acute rejection (within the first 12 months) was more frequent in those who lost their prior allograft from nonadherence, but this association was not apparent in their larger cohort from the more recent era [10]. In our study, patients who lost their first allograft from nonadherence did not experience a higher risk of acute rejection following repeat transplantation, with the types and timing of rejection similar to those who had lost their first allograft from other causes. Given the possibility of misclassification of non-adherence-related second allograft failure as acute rejection, we also evaluated the association between causes of first allograft failure and acute rejection-related second allograft failure. There was no association between nonadherence status and acute rejection-related allograft failure following repeat transplantation, which may be reassuring to clinicians that this highly selected cohort of patients deemed suitable for re-transplantation have comparable "rejection-related" outcomes to other re-transplanted patients.

There are several limitations of note in this study. Importantly, patients who received a second transplant represent a highly selected cohort (i.e., deemed suitable for repeat transplantation), and therefore, the presence of selection bias may have influenced the results of this study. Given the absence of wait-list data, we may have underestimated the proportion of patients with failed first allograft from nonadherence who were considered suitable for a second kidney transplant, considering these patients are likely to be sensitized and wait longer on the transplant waiting list. Access to the wait-list data would be invaluable in revealing the characteristics of those patients who did not progress to both repeat wait-listing and subsequent transplantation. There may be systematic differences in the consideration of re-transplantation and management of patients with failed first allograft from nonadherence versus other causes, potentially modifying the association between causes of first allograft failure and second allograft outcomes. Although multiple confounding factors were adjusted for in these analyses, there were some unmeasured confounders, such as adherence to immunosuppressive agents and clinic appointments, adverse events from immunosuppressive agents, attainment of adequate therapeutic immunosuppressive drug levels, socioeconomic factors, remoteness, psychological conditions that may influence medication adherence, and variation in immunological risk (e.g., pretransplant and *de novo* donor-specific anti-HLA antibodies), which were not collected by the ANZDATA registry. However, given that nonadherence is underreported and under-recognized in routine practice, there is a risk of misclassification bias because of an increased awareness among physicians of treating patients with a documented history of nonadherence, biasing estimates toward an increased effect size. While there may be multiple contributing factors to allograft failure, only the single dominant cause of allograft failure is reported to the ANZDATA registry. As the ANZDATA registry does not verify the accuracy of reporting, misclassification bias can potentially occur. The true incidence of non-adherent-related allograft failure may be underreported, given that nonadherence to immunosuppressive agents may lead to chronic rejection or progressive CAN/IFTA, which are often not reported as attributed to nonadherence. Despite these limitations, this study is a large, contemporary cohort of patients with a second kidney transplant which has evaluated the impact of non-adherence-related first allograft failure and outcome following repeat transplantation.

Although the prevalence of nonadherence has been reported in up to 50% of kidney transplant recipients [18], the true prevalence of nonadherence is likely to be underestimated, because nonadherence is difficult to identify, define, and measure. Most reports rely on either patient's self-report or the presence of objective evidence (e.g., subtherapeutic drug levels, missed clinic appointments). The potential stigma associated with "labeling" patients as suspected of nonadherence may lead to a

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reluctance of patients, families, and clinicians to disclose this behavior, for fear that this could jeopardize clinical care and adversely affect the therapeutic relationship. The lack of universal definition relates to the complexity of the concept, issues including whether nonadherence in transplantation necessitates the conscious omission of immunosuppressive medications (although there remains a lack of consensus regarding the definition of "intentionally missed dosing") or encompasses the omission of any prescribed medications, nonadherence to lifestyle changes such as smoking cessation and missing clinic appointments [19]. However, nonadherent behaviors are likely to be underestimated, as the detection of nonadherence may not be evident until an adverse clinical event occurs, such as acute rejection or suboptimal therapeutic drug levels. Additionally, the degree of nonadherence is difficult to quantify as it fluctuates on a continuum from mild to severe, as with most human behaviors, and vary in nature, frequency, and extent over time [4,6,11,19–21]. It is important to recognize the behavioral patterns of nonadherence, as well as acknowledge that these patterns may evolve with temporal changes in life circumstances.

Nonadherence is a complex and dynamic process. At the clinician level, we should strive to identify at risk patients and consider all potential factors contributing to an individual's risk of nonadherence. Recognition and delineation of intentional versus unintentional nonadherent behaviors may aid clinicians in optimizing tailored interventions and is an important area of research exploring in-depth the foundation of these behavioral patterns. "Unintentional" nonadherence has been reported to account for a majority of nonadherent behaviors [22] and may be related to poor organizational skills or complex medication regimes, which may be addressed with specific measures [5]. Hence, interventions to target modifiable risk factors will likely require a personalized approach using multidimensional strategies. While many of these strategies at an individual level are yet to be demonstrated as cost-effective within the kidney transplant population, a holistic approach for all patients being assessed for and cared for post-kidney transplantation should be considered. In this study, we have shown that the overall and functional allograft outcome of repeat transplantation in patients who had experienced prior allograft failure secondary to nonadherence was similar to other patients, although there was a marginally increase risk of second allograft failure from nonadherence. While this study does not suggests that prior non-adherence-related allograft failure should be considered an absolute barrier to future successful repeat transplantation, it does support that careful patient selection, with additional long-term support and close monitoring in the post-transplant period may be important to ensure optimal allograft outcome in this population.

Authorship

RM, WL and GW: designed the study and/or analyzed the data; all authors contributed to writing of the paper.

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Conflicts of interest

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