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Access to Waitlisting and Posttransplant Outcomes in Patients With Failed Kidney Allografts Secondary to Recurrent Glomerulonephritis

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Background. Recurrent glomerulonephritis (GN) is an important cause of allograft loss after transplantation when GN is the primary cause of kidney failure. Retransplantation after allograft loss from recurrent disease requires careful consideration. We aimed to determine the probability of relisting and the risk of allograft loss after retransplantation in recipients with prior allograft loss from recurrent GN. **Methods.** Using data from the Australia and New Zealand Dialysis and Transplant Registry and multivariable Cox modeling, we compared the probability of waitlisting and allograft loss after second transplantation between those with and without prior allograft loss from recurrent disease. **Results.** Of 3276 patients who received a second kidney transplant, 179 (5%) lost their first allograft from recurrent GN. Between 2006 and 2021, 1524 patients with failed first allografts (6% with recurrent GN, 45% with primary GN but no disease recurrence) were relisted for transplantation. Compared with patients without primary GN, the adjusted hazard ratios (95% confidence intervals) for relisting in patients with primary GN, with and without disease recurrence, were 1.09 (0.88-1.34) and 1.16 (1.05-1.29), respectively. The respective adjusted hazard ratios for allograft loss after repeat transplantation were 0.77 (0.59-1) and 1.02 (0.9-1.16). Of the 81 patients who received a second allograft after losing their first allograft to GN recurrence, 18 patients (22%) also lost their second allograft because of recurrent GN. **Conclusions.** Patients with prior allograft loss from GN recurrence were not disadvantaged, with comparable waitlist potential and allograft outcome after repeat transplantation. However, >20% of those with prior allograft loss from disease recurrence also lost their second allografts from recurrent disease.

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In Australia, glomerulonephritis (GN) is the second leading cause of kidney failure after diabetic kidney disease in patients commencing kidney replacement therapy in 2021,[1] with similar trends observed in the United Kingdom, Canada, and the United States.[2-4] After kidney transplantation, patients who developed recurrent GN were twice as likely to experience premature allograft loss compared with those without recurrent disease, particularly in patients with certain GN subtypes such as membranoproliferative GN.[5-7] Historically, there has been a lack of identifiable risk factors for predicting GN recurrence posttransplant, and combined with the absence of effective interventions to prevent or treat

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recurrent GN, clinicians are often reluctant to consider relisting patients with previous failed allografts because of the fear of GN recurrence after retransplantation.

With the availability of novel therapies for the treatment of GN in the past decade, such as sodium-glucose cotransporter 2 inhibitors, oral budesonide, dual endothelin type A receptor and angiotensin receptor antagonist, and/or humanized anti-CD20 type II monoclonal antibodies for many of the native GNs,[8-10] there is renewed hope that these treatment options can prevent or delay the progression to kidney failure in patients with primary GN or in patients who have developed recurrent GN after kidney transplantation. Patients and clinicians may become less reluctant to consider retransplantation when previous grafts have been lost because of disease recurrence. Despite these factors, the patterns of relisting for transplantation and outcomes after retransplantation of patients with prior failed allografts from recurrent GN are unclear. This study aimed to determine the probability of deceased donor transplant relisting and allograft outcomes after retransplantation in patients with and without prior GN.

MATERIALS AND METHODS

Study Population

Using data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), patients with previous failed first kidney allografts in Australia and New Zealand between 2006 and 2021 were included, including those who have received second kidney-only transplants. Recipients of multiple organ allografts and those with ≥2 prior failed kidney allografts were excluded. Data regarding deceased donor transplant waitlist status after loss of first kidney allografts were extracted from OrganMatch (data available from July 2006 only in Australia), an online clinical transplant system that facilitates organ allocation in Australia. Data on waitlist status were not available for New Zealand recipients.

This study was approved by the Human Research Ethics Committee of The University of Western Australia (reference No. 2023/ET000686). The report of this study was consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Exposure Factor

Patients were categorized into 3 groups according to their primary kidney disease and reasons for their first kidney allograft loss: (1) patients with primary GN and experienced allograft loss from recurrent GN after their first transplant (GN recurrence), (2) patients with primary GN and lost their allografts from other reasons (GN nonrecurrence), and (3) patients without prior GN and lost their allografts because of other causes (non-GN). The causes of allograft loss were prespecified in the ANZDATA registry survey form. In patients with GN recurrence as the cause of first kidney allograft loss, recurrent GN subtypes were also extracted from the registry.

Clinical Outcomes

The primary outcome was repeat transplant potential after first kidney allograft loss, defined as relisting on the deceased donor transplant waitlist (patients who received living donor kidney transplantation were censored at the time of transplantation). The secondary outcome was all-cause allograft loss after a second kidney transplant, defined as the restart of dialysis (after second allograft loss) or death with a functioning allograft. In patients who lost their first kidney allografts from recurrent GN, outcomes of relisting and all-cause allograft survival after second kidney transplantation according to GN subtypes (recurrent IgA nephropathy, membranous GN, focal segmental glomerulosclerosis [FSGS] and membranoproliferative GN [MPGN]) causing first kidney allograft loss were examined.

Data Collection

Baseline patient characteristics at the time of the first kidney allograft and/or at the time of the second kidney transplant were extracted, including age, sex, ethnicity, body mass index, waiting time before the first (and subsequent) transplant, duration of the first allograft, and era. For patients who have received a second kidney transplant, donor and transplant-related characteristics of donor age, donor sex, donor type, total ischemic time, number of HLA mismatches, and acute rejection were extracted from ANZDATA.

Statistical Analyses

Data were expressed as number (proportion), mean and SD, and median and interquartile range, with comparisons between the exposure groups made by the chi-square test, ANOVA, and Mann-Whitney *U* test where appropriate. The associations between causes of prior allograft loss, retransplant potential, and overall allograft loss after a second kidney transplant were examined using adjusted Cox proportional hazard regression analysis. The proportional hazard assumptions of all Cox regression models were checked graphically by plotting Schoenfeld residuals, and there was no evidence of departures from proportional hazards. Covariates included in the multivariable models were selected a priori based on clinical grounds and included age at first kidney allograft loss, sex, race, and era at first kidney allograft loss for the outcome of retransplant potential and for the outcome of overall allograft loss after second kidney transplants, age at second transplant, sex, race, era at second transplant, donor age, donor sex, duration of first allograft, HLA mismatches, total ischemic time, allograft rejection, and comorbidities at time of second kidney transplant were included. Rejection was included as a time-varying covariate and coded as a dichotomous variable that represented the first episode of rejection (cellular or antibody-mediated). Results were expressed as adjusted hazard ratio (aHR) with 95% confidence intervals (95% CIs). In a sensitivity analysis restricted to patients who lost their first kidney allografts to recurrent GN, Kaplan-Meier curves were calculated for retransplant potential and overall allograft survival after second kidney transplants according to GN subtypes of IgA nephropathy, membranous GN, FSGS, and MPGN. Between-group comparisons were made using the log-rank test. The analyses were undertaken using R version 4.3.0 (Vienna, Austria).[11]

RESULTS

Of 10 292 patients with kidney failure from primary GN who received a first kidney allograft during the study period, 351 patients (3%) lost their allografts from recurrent GN, and 3116 patients (30%) lost their allografts from causes other than recurrent GN. Of these, 179 (51%) and 1449 (47%) received a second kidney transplant, respectively (**Figure S1,**

SDC, http://links.lww.com/TXD/A705). Other causes of first allograft loss are shown in **Table S1** (**SDC,** http://links.lww.com/TXD/A705. In the period when waitlist data were available (after July 2006), 158 patients with GN as their primary disease lost their allograft because of recurrent disease, and 100 of these patients (63%) were waitlisted for repeat transplantation, with 81 patients receiving a second kidney transplant (**Figure S2, SDC,** http://links.lww.com/TXD/A705).

In total, 3276 patients received a second kidney transplant. Of these, 179 patients (5%) lost their first kidney allograft because of recurrent GN, and within this group, 81 patients (45%) experienced allograft loss during the follow-up period after the second kidney transplant. Of the 1449 patients with primary GN who lost their first allograft from causes other than GN recurrence, 897 (62%) experienced allograft loss during the follow-up period after a second kidney transplant (Figure 1). These results, according to GN type, in first and second transplants are shown in **Table S2** (**SDC,** http://links.lww.com/TXD/A705). Table 1 shows the characteristics of patients who received second kidney allografts, stratified by exposure groups. A greater proportion of the GN recurrence group were males of Asian ethnicity and received their second kidney transplant in the most recent era (post-2011) compared with GN nonrecurrence and non-GN groups. The mean age at first allograft loss was similar between the 3 groups.

Association Between Causes of First Kidney Allograft Loss and Repeat Transplant Listing

Of the 3051 patients with failed first kidney allografts after July 2006, 1501 patients (49%) were subsequently enrolled on the deceased donor transplant waitlist, 1339 patients (44%) were never relisted, and 211 patients (7%) received a living donor transplant. In the GN recurrence group, which totaled 158 of these patients, 100 (63%) were enrolled on the deceased donor transplant waitlist. This compared with 688 (53%) and 736 patients (46%), respectively, in the GN nonrecurrence and non-GN groups. **Table S3** (**SDC,** http://links.lww.com/TXD/A705) shows the characteristics of patients in the GN recurrence group who were and were not relisted. The only significant difference between the groups was the median age of failure of the first allograft. Those who were relisted were younger than those who were not (median age 53 versus 47; $P = 0.002$).

Compared with patients in the non-GN group, the aHR (95% CI) of repeat waitlisting in the GN recurrence and GN nonrecurrence groups were 1.09 (0.88-1.34) and 1.16 (1.05-1.29), respectively (Table 2).

Association Between Causes of First Kidney Allograft Loss and All-cause Allograft Loss After Second Kidney Transplant

During a median (interquartile range) allograft follow-up period of 5.7 y (1.7–11.9), 2020 patients (62%) lost their second kidney allograft. Eighty-one patients (45%) who experienced graft loss from recurrent GN lost their second kidney allografts (from any cause). This compared with 897 patients (62%) in the GN nonrecurrence group and 1042 patients (63%) in the non-GN group ($P < 0.01$). Of the 81 patients in the GN recurrence group who lost their second allograft, the cause of allograft loss was recurrent GN in 18 cases (22%; **Table S4, SDC,** http://links.lww.com/TXD/A705). In the GN without recurrence group, the cause of allograft loss in the second allograft was GN recurrence in 33 patients (4%).

The risk of all-cause allograft loss in the second kidney allograft was similar between the 3 exposure groups. The aHR (95% CI) for second kidney allograft loss in patients in the GN recurrence and GN nonrecurrence groups were 0.77 (0.59-1.00) and 1.02 (0.90-1.16), respectively, compared with patients in the non-GN group (Table 3).

Sensitivity Analysis: Repeat Transplant Waitlisting and Repeat Transplant Allograft Survival

Figure 2 shows Kaplan-Meier all-cause allograft survival after the second kidney transplantation, stratified by recurrent GN subtypes (log-rank test $P = 0.58$). The 1, 3, and 5-y allograft survivals after second kidney transplantation for patients who lost their first kidney allograft because of recurrent IgA nephropathy were 95%, 91%, and 87%, respectively. This is compared with 92%, 92%, and 85% for those who lost their first kidney allograft from membranous GN; 85%, 85%, and 77% for those who lost their first allograft from FSGS; and 96%, 76%, and 76% for those who lost their first allograft from MPGN.

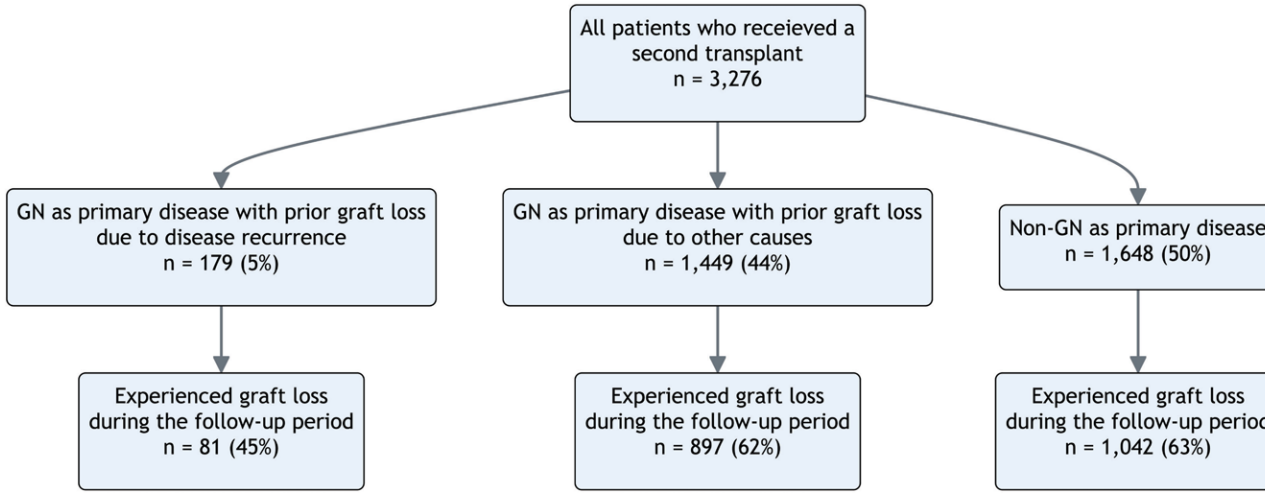

FIGURE 1. Flow diagram of the study cohort of the 3276 patients who received second kidney transplants. GN, glomerulonephritis.

TABLE 1.

Baseline characteristics of patients who received a second allograft

Characteristic	GN recurrence group (N = 179)	GN without recurrence group (N = 1449)	Non-GN group (N = 1648)	*P*[a]
Age, y	43 (33–55)	43 (33–52)	41 (29–51)	**<0.001**
Sex				**<0.001**
Female	44 (25%)	461 (32%)	756 (46%)	
Male	135 (75%)	988 (68%)	892 (54%)	
Ethnicity				
Caucasian	142 (79%)	1222 (84%)	1476 (90%)	
Asian	21 (12%)	104 (7.2%)	39 (2.4%)	
Pasifika	1 (0.6%)	7 (0.5%)	9 (0.5%)	
Aboriginal or Torres Strait Islander	1 (0.6%)	39 (2.7%)	28 (1.7%)	
Māori	0 (0%)	7 (0.5%)	4 (0.2%)	
Other	14 (7.8%)	70 (4.8%)	92 (5.6%)	
Transplant duration, y	8 (4–13)	5 (2–11)	6 (1–12)	**0.004**
All-cause graft loss	81 (45%)	897 (62%)	1042 (63%)	**<0.001**
Death	48 (27%)	712 (49%)	818 (50%)	**<0.001**
Rejection	55 (31%)	255 (18%)	292 (18%)	**<0.001**
Era of second transplant				**<0.001**
≤1994	25 (14%)	559 (39%)	672 (41%)	
1995–2010	76 (42%)	426 (29%)	475 (29%)	
≥2011	78 (44%)	464 (32%)	501 (30%)	
Transplant duration of first transplant, y	8 (4–12)	4 (0–10)	4 (0–10)	**<0.001**
Era of failure of first graft				**<0.001**
≤1994	35 (20%)	643 (44%)	775 (47%)	
1995–2010	91 (51%)	487 (34%)	501 (30%)	
≥2011	53 (30%)	319 (22%)	372 (23%)	
Age at failure of first transplant	41 (28–52)	39 (30–49)	38 (25–48)	**<0.001**
Total ischemic time, h	11 (5–15)	12 (7–16)	12 (6–17)	0.2
Missing	11	314	389	
HLA-mismatches				0.13
0	15 (8.6%)	95 (7.6%)	125 (8.9%)	
1	19 (11%)	184 (15%)	227 (16%)	
2	45 (26%)	345 (28%)	364 (26%)	
3	31 (18%)	220 (18%)	287 (20%)	
4	30 (17%)	201 (16%)	202 (14%)	
5	27 (16%)	144 (11%)	148 (11%)	
6	7 (4.0%)	64 (5.1%)	49 (3.5%)	
Missing	5	196	246	
Delayed graft function	36 (23%)	417 (39%)	419 (36%)	**<0.001**
Missing	22	371	490	

Data are presented as median (IQR) or n (%). Values in bold indicate statistical significance at $p < 0.05$.
[a]Kruskal-Wallis rank-sum test; Pearson's chi-square test.
GN, glomerulonephritis; IQR, interquartile range.

Figure 3 shows Kaplan-Meier relisting events after the first kidney allograft loss, stratified by recurrent GN subtypes (log-rank test $P = 0.78$). The probability of relisting at 1 and 3 y after second kidney transplantation for patients who lost their first kidney allograft because of recurrent IgA nephropathy was 46% and 64%. This is compared with 40% and 67% for those who lost their first kidney allograft from membranous GN, 30% and 62% for those who lost their first allograft from FSGS, and 30% and 43% for those who lost their first allograft from MPGN.

DISCUSSION

In this large binational study from Australia and New Zealand evaluating the relisting potential and allograft outcomes after second kidney transplantation in patients who lost their first kidney allografts, patients who lost their first allografts from recurrent GN had a similar probability of repeat deceased donor kidney waitlisting and second kidney allograft survival compared with those who lost their first kidney allografts from causes other than recurrent GN. The likelihood of repeat waitlisting and second kidney allograft survival were similar across the 4 most common causes of recurrent GN subtypes causing first kidney allograft loss. However, among those who lost a second transplant (after losing their first allograft to GN recurrence), >20% of allograft loss was again because of GN recurrence, suggesting that although our overall findings were reassuring, clinicians and patients with recurrent GN will still need to be cognizant of the risk of losing the second kidney allograft from the same disease process.

Allograft loss from GN recurrence is one of the most feared complications of kidney transplantation in those with GN as their primary cause of kidney failure. In a registry analysis from Australia and New Zealand comprising 6597

TABLE 2.

Adjusted HRs for repeat waitlisting after a failed first allograft

Characteristic	HR	95% CI	*P*
Primary disease			**0.021**
Non-GN group	–	–	
GN recurrence group	1.09	0.88-1.34	
GN without recurrence group	1.16	1.05-1.29	
Age at failure of first transplant	0.97	0.97-0.97	**<0.001**
Sex			0.4
Female	–	–	
Male	0.96	0.86-1.06	
Ethnicity			**<0.001**
Caucasian	–	–	
Asian	1.08	0.92-1.28	
Pasifika	0.50	0.35-0.72	
Aboriginal or Torres Strait Islander	0.44	0.33-0.58	
Māori	0.74	0.41-1.34	
Other	1.39	1.14-1.69	
Era of failure of first transplant			**<0.001**
2006–2011	–	–	
2012–2016	1.18	1.04-1.34	
2017–2021	1.30	1.15-1.48	

Values in bold indicate statistical significance at $p < 0.05$.
CI, confidence interval; GN, glomerulonephritis; HR, hazard ratio.

TABLE 3.

Adjusted HRs for all-cause graft loss in second allograft

Characteristic	HR	95% CI	*P*
Primary disease			0.076
Non-GN group	–	–	
GN recurrence group	0.77	0.59-1.00	
GN without recurrence group	1.02	0.90-1.16	
Recipient age (at time of 2nd transplant)	0.99	0.99-1.00	**0.009**
Recipient sex			0.6
Female	–	–	
Male	1.04	0.91-1.18	
Duration of first transplant, y	0.99	0.98-1.00	0.052
Years on dialysis (ever)	1.03	1.01-1.05	**0.002**
Recipient diabetes			**0.050**
No	–	–	
Type 1: insulin dependent	1.40	0.96-2.03	
Type 2	1.37	1.00-1.87	
Recipient cerebrovascular disease			**0.042**
No	–	–	
Yes	1.37	1.02-1.85	
Recipient peripheral vascular disease			0.13
No	–	–	
Yes	1.23	0.94-1.61	
Recipient coronary artery disease			**0.007**
No	–	–	
Yes	1.36	1.09-1.68	
Donor age	1.01	1.01-1.02	**<0.001**
Donor sex			0.093
Female	–	–	
Male	0.90	0.79-1.02	
Transplant type			0.5
Deceased	–	–	
Living	1.08	0.86-1.36	
Total ischemic time, h	1.02	1.01-1.03	**0.004**
No. of HLA mismatches	1.02	0.98-1.06	0.4
Rejection	1.75	1.50-2.04	**<0.001**
Era			**<0.001**
≤1994	–	–	
1995–2010	0.81	0.68-0.97	
≥2011	0.45	0.36-0.58	

Values in bold indicate statistical significance at $p < 0.05$.
CI, confidence interval; HR, hazard ratio.

patients with biopsy-proven primary GN who had received kidney transplants, 10% of recipients with the most common GN subtypes in IgA nephropathy, membranous GN, MPGN, and FSGS experienced disease recurrence after transplantation. Of those with recurrent disease, almost 45% lost their kidney allografts during follow-up, and those with recurrent MPGN had the poorest allograft survival.[5] These findings have been corroborated in other large registry and single-center studies, where up to 90% of those with primary GN were reported to experience recurrent disease in the allograft. Patients with recurrent MPGN (especially C3GN) and FSGS had the most aggressive course, with the risk of death-censored allograft loss 5 to 7 times higher than those without recurrent disease.[12]

Allograft outcomes after repeat transplantation in patients who have lost their first allografts from GN recurrence are poorly defined. A greater understanding of this issue is critical because disease recurrence in the second allograft could again lead to premature allograft loss and mortality, potential wastage of a donor organ, and increased allosensitization, the latter of which could markedly reduce the probability of another kidney transplant. However, the risk of second kidney allograft loss in patients who lost the first allografts from GN recurrence is similar to those without GN, >20% of allograft loss in the second kidney transplant in these patients was attributed to GN recurrence. However, in patients with primary GN who lost their first allografts from causes other than GN recurrence, only 4% of second allograft loss was attributed to GN recurrence. This suggests that specific GN genotype-phenotypes may be more susceptible to disease recurrence. However, selection bias is likely as patients deemed to be at high risk of GN recurrence may not be considered suitable for repeat transplantation. The ANZDATA registry does not collect information on specific GN characteristics, the presence of high-risk genetic mutations, or treatment (prior and current) of the GN disease process, which may have influenced the clinical likelihood of disease recurrence in these patients and could potentially discriminate patients with primary GN who may be more prone to GN recurrence after transplantation.

The eligibility for deceased donor kidney transplant waitlisting is dependent on multiple factors, including projected survival posttransplant, comorbidities, and psychosocial factors.[13] Although patients with primary GN can experience disease recurrence posttransplantation, retransplantation is not contraindicated in these patients. However, in patients who have lost their first kidney allograft because of GN recurrence, the decision to relist often requires shared decision-making between clinicians and patients, balancing the probability of disease recurrence with the expected benefits of retransplantation. In our study, the probability of repeat waitlisting of patients with prior failed allograft from GN recurrence

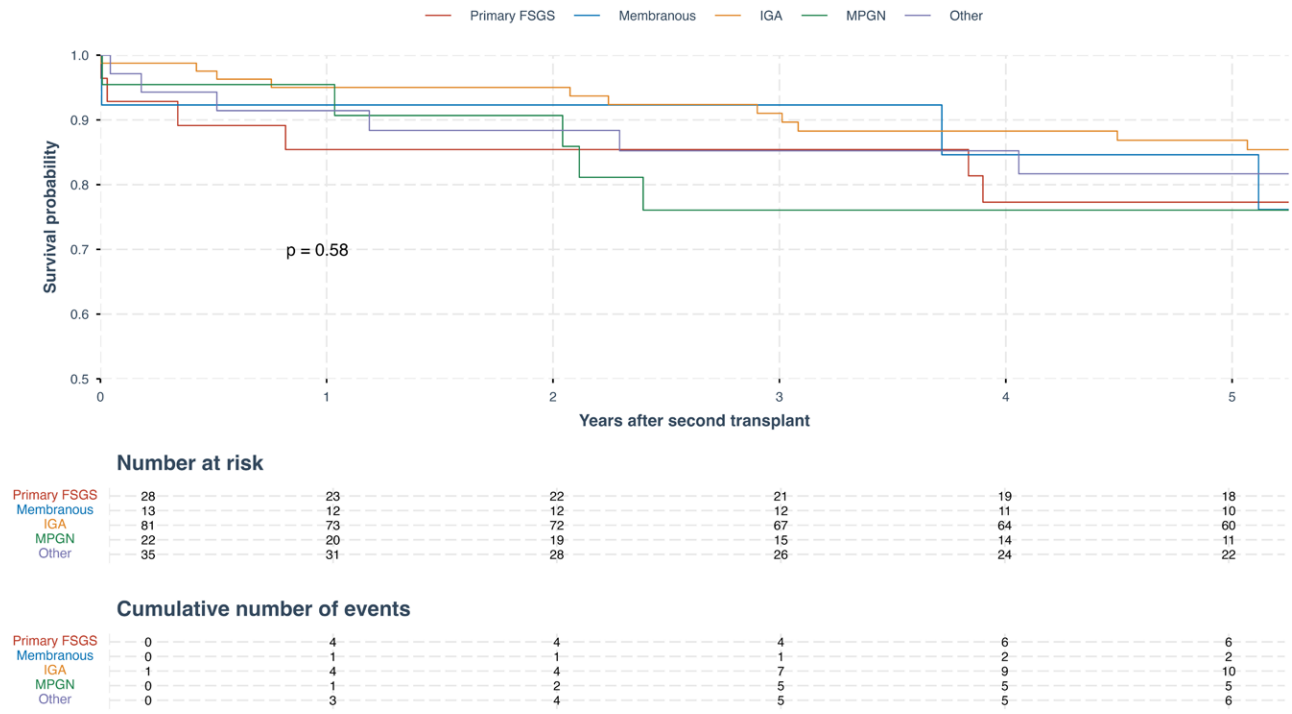

FIGURE 2. Kaplan-Meier survival curves for all-cause allograft survival after second kidney transplantation, stratified by glomerulonephritis subtype. FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

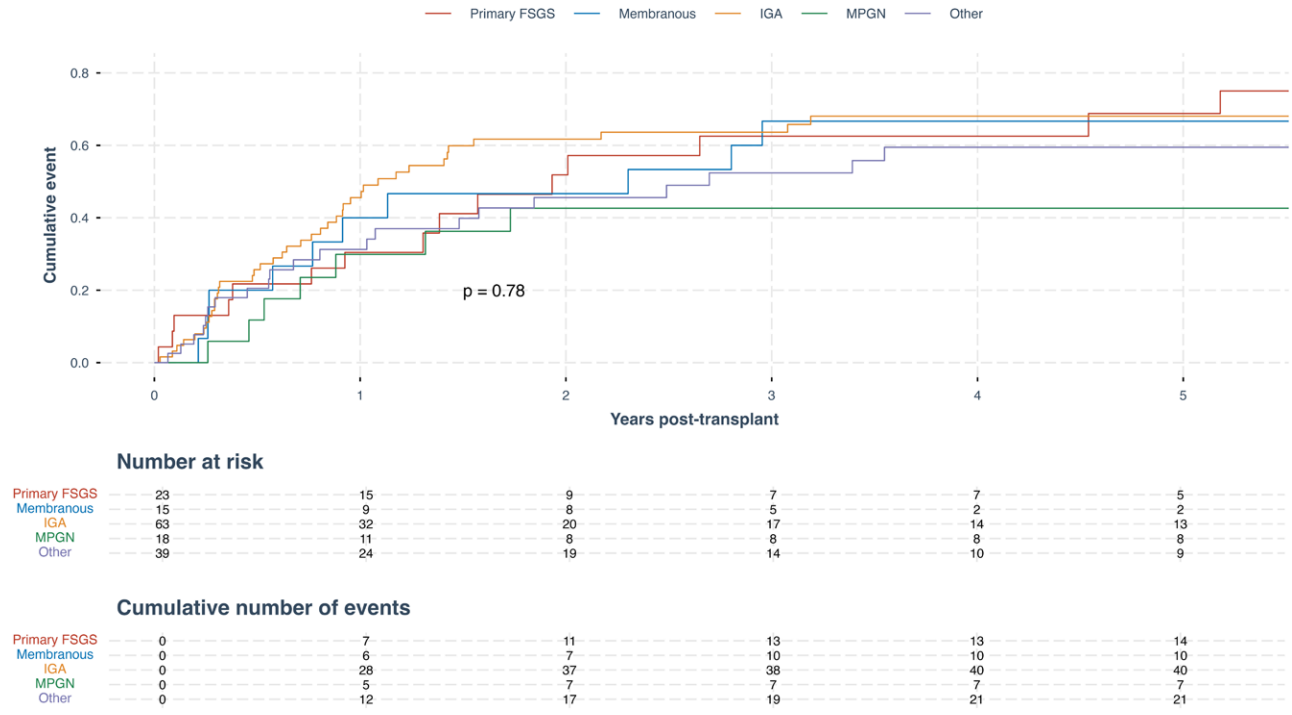

FIGURE 3. Kaplan-Meier cumulative incidence curves for deceased donor relisting after first kidney allograft loss, stratified by glomerulonephritis subtype. FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

was similar to those with non-GN causes of kidney failure, independent of other patient characteristics known to affect repeat transplant waitlisting, including age and comorbidities. This finding indicates that the loss of previous kidney allografts from GN recurrence is not necessarily an impediment to the consideration of repeat transplantation.

Currently, treatment options and optimal immunosuppressive regimen(s) for GN recurrence post–kidney transplantation are largely extrapolated from studies in the general population. The efficacy of these treatment options in kidney transplantation is limited to case series or cohort studies.[14-17] Given the surge of clinical trials that evaluate the development

and efficacy of novel drugs in the treatment of primary GN, it is possible that these drugs may translate into safe and effective treatment strategies in the treatment or prevention of GN recurrence after transplantation for high-risk GN subtypes.

The completeness of our data suggests that selection and ascertainment biases between the exposure and outcome measures were likely reduced. However, there are several limitations that should be considered when interpreting the study findings, including selection, reporting, confounding, and information biases. As this was a retrospective registry-based analysis, granular detail was lacking, particularly in relation to the spectrum of disease severity, the specific treatments administered, and genetic and histological data. Furthermore, the relatively low number of patients with second transplants after GN recurrence limited our ability to detect differences between groups. This study was conducted exclusively in patients from Australia and New Zealand, so these results may not be generalizable to other regions. Although multiple confounders were adjusted for in the analysis, there could be unmeasured factors such as the systematic differences or specific reasons in acceptance for relisting/retransplantation of patients who lost their first allografts because of GN recurrence, medication nonadherence, treatment of transplant complications including GN recurrence, and the severity of recipient comorbid conditions, all of which could potentially modify the association between exposure and outcomes. There may also be differences in the genotype–phenotype of those with primary GN and the accurate ascertainment of the causes of allograft loss (from GN recurrence or other causes) is not required by the registry.

Although the epidemiology of recurrent GN (including the prevalence and outcomes) is well described, the risk factors for and treatment of recurrent GN remain unclear. Despite these uncertainties, our study shows that patients with prior allograft loss from GN recurrence are not disadvantaged from being relisted for transplantation or allograft survival after repeat transplantation. However, GN recurrence remains an important cause of allograft loss after second transplantation. A greater understanding of the underlying bimolecular mechanisms of GN that affect both native and transplanted kidneys, combined with the advancement of therapies available for this disease, may allow adjustment of the individualized treatment strategy to prevent or treat recurrent GN in the allograft, thus optimizing kidney transplant outcomes.

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