Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes

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Recurrent glomerulonephritis after kidney transplantation is a feared complication because it is unpredictable and may have a negative impact on graft outcomes. To better understand this we collected data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry accumulated over 30 years. The incidence, risk factors, and outcomes of recurrent glomerulonephritis in transplant recipients were determined using adjusted Cox proportional hazard and competing risk modeling. A total of 6,597 recipients with biopsy-proven glomerulonephritis as the primary cause of end-stage kidney disease were followed for 51,871 person-years (median duration 7.7 years). The four most common types of glomerulonephritis were IgA nephropathy in 2501 patients, focal segmental glomerulosclerosis (FSGS) in 1403, membranous in 376, and membranoproliferative (MPGN) nephropathy in 357 patients. Among these four types, recurrence was reported in 479 of 4637 patients, and of these, 212 lost their allograft due to recurrence. Older age at transplantation (adjusted hazard ratio [per year increase] 0.96 [95% confidence interval 0.95 – 0.97]) was associated with a lower risk of recurrence. Significantly, the five-year graft survival was 30% for recipients with recurrent MPGN and 57-59% for recipients with FSGS, IgA, and membranous nephropathy. Transplant recipients with recurrent disease were twice as likely to lose their allografts compared to those without recurrence (adjusted hazard ratio 2.04 [1.81-2.31]). Thus, recurrent glomerulonephritis remains a significant cause of graft loss in transplant recipients.

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Glomerulonephritis (GN) is one of the leading causes of end-stage kidney disease (ESKD) worldwide.[1,2] In Australia and New Zealand, GN accounts for 20% of new cases of ESKD,[3] but is the most common indication for kidney transplantation.[4] It is well known that GN may recur after kidney transplantation, with reported rates varying widely, from 2.6% to 50% in previous studies.[2,5–9] This disparity may be related to a number of factors including variable follow-up times, incomplete biopsy data, different diagnostic criteria and population characteristics, variable thresholds for transplantation, and inconsistent reporting practices.[10] Several factors including male gender,[5,11] younger recipient age,[5,8] living related donors,[8] and closer HLA matching[12] have been shown to be associated with disease recurrence in the transplanted population, but the risk factors identified have also been inconsistent.

GN recurrence is of concern to clinicians and patients because it is associated with adverse allograft outcomes including allograft loss. Previous studies have reported an excess risk of allograft loss by about 50% among recipients who experienced recurrent glomerular disease compared with those who did not.[11,13,14] Recurrent GN is the fourth most common cause of allograft loss after acute rejection, chronic allograft nephropathy, and death with a functioning allograft.[11] A report of data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) demonstrated an average risk of 8.4% recurrence-related allograft loss within 10 years after kidney transplantation.[11] However, the reported allograft loss rates attributed to disease recurrence vary between 7% and 55% internationally, largely influenced by differing follow-up times and the era of transplantation.[5,7,9,15–17] Given the uncertainties regarding the trajectory of disease recurrence and progression in

recipients with biopsy-proven GN as their primary cause of ESKD, the objectives of this study, using 30 years of data from the ANZDATA Registry, were to determine the incidence of biopsy-proven recurrent GN and predictors of disease recurrence in kidney transplant recipients. We also compared the risk of death censored and overall allograft loss in patients with and without recurrent GN, and by GN subtypes.

RESULTS

Of the 17,549 patients who received their first kidney transplant between 1985 and 2014, GN was the cause of ESKD in 7968 (45%) of patients (6597 [82.7%] biopsy-proven and 1371 [17.3%] non-biopsy proven) (Figure 1). Of those with biopsy-proven GN, IgA nephropathy was the most frequent disease subtype ($n = 2501$, 37.9%), followed by focal and segmental glomerulosclerosis (FSGS) ($n = 1403$, 21.3%), membranoproliferative glomerulonephritis (MPGN) ($n = 376$, 5.7%), and membranous GN ($n = 357$, 5.4%).

Characteristics of the study cohort

The baseline characteristics of the cohort ($n = 7968$) are shown in Table 1. Overall, 312 (3.92%) were pediatric transplant recipients (age $\leq$ 18 years). The mean (SD) and median (interquartile range [IQR]) ages of the cohort were 43.3 (14.5) and 44.0 (22.3) years, respectively. Recipients with biopsy-proven GN recurrence were likely to be younger (36.9 years vs. 43.8 years), more likely to be male (72% vs. 67.2%), and to have received a living donor allograft (40.9% vs. 31.6%). There were no significant differences in ethnicity, weight at transplant, recipient comorbidities, donor gender, delayed allograft function, or era of transplantation between patients who developed recurrent GN and those who did not.

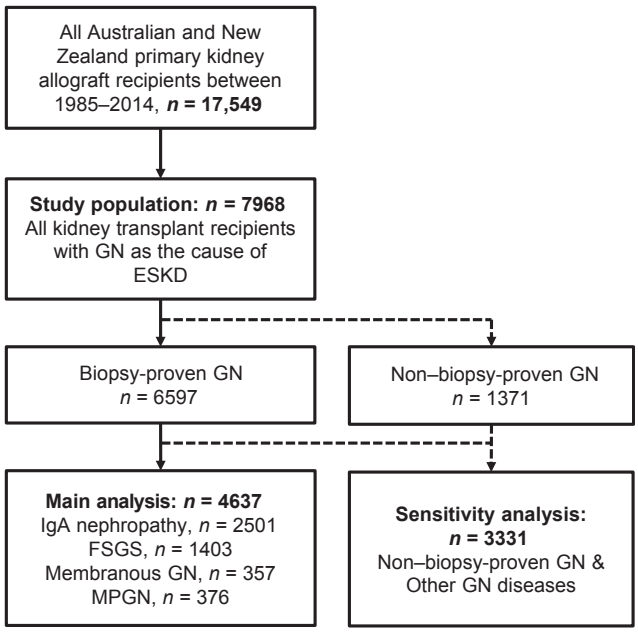

Figure 1 | Cohort profile. ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis.

Incidence of recurrent GN

Over a follow-up period of 31,561 person-years, 479 (10.3%) of 4637 recipients with FSGS, IgA nephropathy, membranous GN, and MPGN were reported to have GN recurrence, with the likelihood of recurrence varying by GN. Approximately 11.8%, 15.6%, and 18.9% of recipients with MPGN experienced disease recurrence at 5, 10, and 15 years after transplantation. This compared with 5.1%, 10.1%, and 15% for recipients with IgA nephropathy, 7.3%, 9.0%, and 11% for those with FSGS, and 10%, 16%, and 18% for recipients with membranous nephropathy at 5, 10, and 15 years after transplantation (log-rank P value = 0.02) (Figure 2).

Risk factors for recurrence

Age at transplantation at baseline was identified as an independent risk factor for any GN recurrence after adjusting for the effects of donor source (living vs. deceased), hypertension, HLA mismatches, panel reactive antibody, time on dialysis, and competing events for death and other causes of non–GN-related allograft loss (Table 2). For every year increase in age at transplantation, there was a 2% reduction in the risk of disease recurrence (adjusted hazard ratio [HR]: 0.96; 95% CI: 0.94–0.97; $P < 0.001$) (Figure 3). The linear and inverse relationship persisted until the age of transplantation reached 40 years. Other factors included steroid use at baseline (adjusted HR: 0.54; 95% CI: 0.37–0.76; $P < 0.001$) and ischemic time (per hour increase) (adjusted HR: 0.97; 95% CI: 0.96–0.99).

For type-specific risk analyses, younger age at transplantation was an independent risk factor for recurrence of IgA nephropathy and FSGS. For every year increase in recipient age, there was a corresponding reduction by 6% and 5% in the risk of recurrence among those with IgA nephropathy (adjusted HR: 0.94; 95% CI: 0.92–0.96; $P < 0.001$) and FSGS (adjusted HR: 0.95; 95% CI: 0.94–0.96; $P < 0.001$). However, steroid use at baseline (adjusted HR: 0.30; 95% CI: 0.20–0.46; $P < 0.001$) and longer total ischemic time (adjusted HR: 0.97; 95% CI: 0.95–0.99; $P = 0.004$) were factors protective against recurrence only for recipients with IgA nephropathy but not FSGS.

Disease recurrence and allograft loss

Over a follow-up period of 31,647 person-years, 349 (72.9%) of the 479 recipients whose disease recurred lost their allografts and 141 (29.4%) died. GN recurrence was associated with an increased risk of overall and death-censored allograft loss. Recipients who developed recurrent GN were twice as likely to lose their allografts compared with those who did not experience disease recurrence. The adjusted HRs (95% CI) for death-censored and overall allograft loss for those who experienced recurrent GN compared with those who did not were 3.19 (2.68–3.80) and 2.04 (1.81–2.31), respectively (Table 3). The probability of overall and death-censored allograft loss in recipients with and without disease recurrence is shown in Figure 4. When recurrence was treated as a time-varying covariate, the HRs for death-censored and