Long-term graft outcomes and patient survival are lower posttransplant in patients with a primary renal diagnosis of glomerulonephritis

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Glomerulonephritis (GN) is the primary diagnosis in 20% to 40% of patients receiving a renal transplant. Here we studied patient survival and graft outcomes in patients with GN transplanted in the UK. UK Renal Registry data were used to analyze patient survival and graft failure in incident transplant patients between 1997 to 2009 who had a diagnosis of primary GN, in comparison to patients transplanted with adult polycystic kidney disease (APKD) or diabetes. Multivariable regression analysis adjusted for age, sex, donor type, ethnicity, donor age, time on dialysis, human leukocyte antigen mismatch, cold ischemic time, and graft failure (for patient survival). Patients were followed up through December 2012. Of 4750 patients analyzed, 2975 had GN and 1775 APKD. Graft failure was significantly higher in membranoproliferative glomerulonephritis (MPGN) type II (hazard ratio: 3.5, confidence interval: 1.9–6.6), focal segmental glomerulosclerosis (2.4, 1.8–3.2), MPGN type I (2.3, 1.6–3.3), membranous nephropathy (2.0, 1.4–2.9), and IgA nephropathy (1.6, 1.3–2.0) compared to APKD. Survival was significantly reduced in patients with MPGN type II (4.7, 2.0–10.8), and those with lupus nephritis (1.8, 1.1–2.9). Overall graft failure for patients with GN was similar to those with diabetes. Thus, in comparison to outcomes in APKD, graft survival is significantly lower in most GNs, with variation in outcomes between different GNs. This information should assist in pretransplant counseling of patients. Further study is required to understand the reduced survival seen in lupus nephritis and MPGN type II, and to improve overall graft outcomes.

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Glomerulonephritis (GN) is a major cause of end-stage renal disease (ESRD), and is the primary diagnosis in 20% to 40% of patients receiving a renal transplant.[1] The development of new immunosuppressive therapies has resulted in a significant increase in both short- and long-term graft survival from both living- and deceased-donor transplants over the last 3 decades.[2] These therapies have largely been targeted toward controlling acute and chronic rejection, but have had limited impact on the incidence and outcome of recurrent and *de novo* GN after transplantation.[3] Data from a number of studies suggest the cumulative incidence of recurrent GN varies from 2% to 18%.[4,5] The impact of recurrence on graft survival is significant. The Renal Allograft Disease Registry in the United States reported that posttransplant allograft survival at 8 years was significantly different for patients with recurrent GN versus no recurrence (34% vs. 53%; $P = 0.003$).[3] A more recent report from the Canadian registry looked at 2026 sequential renal transplant recipients and showed the estimated graft survival at 15 years posttransplant was significantly reduced in patients with posttransplant GN (10.2% vs. 69.7%; $P < 0.0001$)[6] as compared to those who did not develop posttransplant GN. Consequently, recurrence of GN is the third most frequent cause of allograft loss at 10 years, after chronic rejection and death with a functioning graft, and is therefore an important cause of allograft loss.[7,8]

While clinical recurrence has been reported for most types of GN, the frequency of recurrence may vary between the specific GNs. Focal segmental glomerulosclerosis (FSGS) is reported to recur after transplantation in approximately 20% to 30% of cases,[9,10] which is similar to that reported for membranous nephropathy (10%–30%)[11–13] and membranoproliferative glomerulonephritis (MPGN) type I (10%–30%).[11,14,15] Even higher rates of recurrence are reported for IgA nephropathy (20%–60%)[11,16,17] and MPGN type II (50%–100%).[14,15,18] Despite the significant risk of disease recurrence and increasing prevalence of patients transplanted with GN, there is currently a paucity of published data on the long-term outcomes after first renal transplant for specific GNs.

The primary aim of this study is to determine the risk of graft loss and patient survival for specific GNs, by comparing graft outcomes and survival of patients transplanted in the

United Kingdom with a primary diagnosis of GN with those of a comparator group in whom the primary renal disease does not recur posttransplantation (adult polycystic kidney disease [APKD]).

RESULTS

Comparing GN outcomes with APKD patients

Of 5515 patients identified as being eligible for this study (based on the inclusion criteria), 14% (765 patients) were excluded from the analysis due to having either incomplete data for cold ischemic time or human leukocyte antigen (HLA) mismatch. Missing data were equally distributed across the GN group and the APKD group with no statistical differences. The distribution and categorization of primary renal diagnoses among the remaining 4750 patients based on European Renal Association–European Dialysis and Transplant Association coding are shown in Table 1, and the demographic characteristics in Table 2.

Overall there were 2975 patients in the GN group and 1775 patients in the APKD control group. The median follow-up time for graft failure was 5.5 years (interquartile range: 3.8–8.3) and for patient survival was 5.9 years (interquartile range: 4.2–8.9). Patients in the GN group were significantly younger (median age 45 vs. 53; $P < 0.0001$), and although both groups had a male preponderance, this was greater in the GN group (66.7% vs. 54.5%; $P < 0.0001$). There were also more ethnic minorities in the GN group and more living kidney transplantation (33.9% vs. 28.5%; $P < 0.0001$), though patients with APKD had more preemptive transplantation (16.1% vs. 12.3%; $P = 0.0001$). There was no significant difference in HLA mismatch between the 2 groups, and while cold ischemic times were significantly different (14.0 vs. 14.8; $P < 0.0001$), a separate sensitivity analysis showed that the difference in cold ischemic time disappeared once the higher rates of living donation seen in the GN group were accounted for.

Unadjusted 10-year graft survival across the range of GNs analyzed varied with a range of 56.3% to 83.9% (Figure 1). Of these, MPGN type II and FSGS had the worst outcomes at 56.3% and 65.7%, respectively, while those in the APKD comparison group had a 10-year graft survival of 84.8% (Supplementary Table S1 online).

The 10-year risk of graft failure in the multivariable analysis was significantly higher in patients with MPGN type II (hazard ratio [HR]: 3.5, confidence interval [CI] 1.87–6.55), FSGS (HR: 2.39, CI 1.78–3.22), MPGN type I (HR: 2.33, CI 1.63–3.33), membranous nephropathy (HR: 1.99, CI 1.38–2.86), GN histologically proven (HR: 1.68, CI 1.31–2.17), lupus nephritis (HR 1.64, CI 1.13–2.4), and IgA nephropathy (HR: 1.59, CI 1.27–1.99). While MPGN type II had the worst outcomes, the confidence interval for MPGN type II is particularly wide reflecting the small cohort. Graft outcomes in patients with granulomatosis with polyangiitis or those labeled as having crescentic GN did not show any significant difference. Analysis of graft failure using a competing risk model did not show any differences, with subhazard ratios produced similar to those shown in Table 3.

Patient survival

Unadjusted 10-year patient survival derived from Kaplan–Meier analysis for the APKD control group was 80.7%. This was similar to that of the different GNs analyzed ranging from 75.6% for MPGN type II to 85.6% for IgA nephropathy (Figure 2 and Supplementary Table S2).

From the adjusted model, however (Table 4), 2 of the GNs analyzed were seen to have significantly reduced 10-year survival compared to APKD, with MPGN type II (HR: 4.7, CI 2.0–10.8) and lupus nephritis (HR: 1.8, CI 1.1–2.9) groups having reduced survival. These findings were seen even after adjusting for graft failure.

Comparison with patients with diabetes mellitus

Separate analyses were performed to compare outcomes of the GN group ($n = 2975$) with those of patients with diabetes mellitus (DM) ($n = 1873$). Baseline patient characteristics of

Table 1 | Number and percentage of patients analyzed by primary renal diagnosis in multivariable model, with the corresponding number of deaths, failed grafts, and median follow-up time

Primary renal diagnosis	Total number of patients with complete data, multivariable model	% of total sample	Number of graft failures[a]	Number of deaths[b]	Median follow-up (to death) in years
APKD	1775	37.4	179	221	5.9
Crescentic GN	100	2.1	15	15	5.3
FSGS	297	6.3	65	32	5.4
GN histologically not examined	258	5.4	26	34	6.2
GN histologically proven	557	11.7	98	75	6.4
IgA nephropathy	1069	22.5	163	103	6.0
Lupus nephritis	190	4	39	22	5.8
Membranous nephropathy	183	3.9	36	29	6.2
MPGN type I	171	3.6	39	22	6.3
MPGN type II	30	0.6	11	6	6.1
GPA	120	2.5	15	17	6.7
Total	4750	100	686	576	5.8

APKD, adult polycystic kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; MPGN, membranoproliferative glomerulonephritis.
[a]Over a maximum follow-up time of 10 years.
[b]With functioning graft or after return to dialysis.