Quantifying association of early proteinuria and estimated glomerular filtration rate changes with long-term kidney failure in C3 glomerulopathy and immune-complex membranoproliferative glomerulonephritis using the United Kingdom RaDaR Registry

OPEN

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Abstract

Introduction: C3 glomerulopathy (C3G) and immune-complex membranous proliferative glomerulonephritis (IC-MPGN) are rare disorders that frequently result in kidney failure over the long-term. Presently, there are no disease-specific treatments approved for these disorders, although there is much interest in the therapeutic potential of complement inhibition. However, the limited duration and necessarily small size of controlled trials means there is a need to quantify how well short-term changes in estimated glomerular filtration rate (eGFR) and proteinuria predict the clinically important outcome of kidney failure.

Methods: We address this using longitudinal data from the UK Registry of Rare Kidney Diseases (RaDaR) involving retrospective and prospective data collection with linkage to hospital laboratories via automated feeds of 371 patients. Analyses of kidney survival were conducted using Kaplan–Meier and Cox regression with eGFR slope estimated using linear mixed models.

Results: In a median of 11.0 (inter quartile range 7.4-15.1) years follow-up, 148 patients (40%) reached kidney failure. There was no significant difference in progression to kidney failure between C3G and IC-MPGN groups. Baseline urine protein-creatinine ratio (UPCR), although high, was not associated with kidney failure in either group. Two-year eGFR slope had a modest association with kidney failure. In contrast, both 20%−50% and 50 mg/mmol reductions in UPCR between 0-12 months were associated with lower kidney failure risk in both groups. Notably, those with a UPCR under 100 mg/mmol at 12 months had a substantially lower risk of kidney failure (hazard ratio 0.10 (95% confidence interval 0.03-0.30).

Conclusions: Overall, proteinuria a short time after diagnosis is strongly associated with long-term outcomes and a UPCR under 100 mg/mmol at one year is associated with a substantially lower kidney failure risk.

Kidney International (2025) ■, ■–■; https://doi.org/10.1016/j.kint.2025.06.003

KEYWORDS: C3; C3 glomerulopathy; complement; dense deposit disease; membranoproliferative glomerulonephritis; rare kidney disease registry

Lay Summary

C3 glomerulopathy (C3G) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare kidney conditions that frequently lead to kidney failure (KF). Little is known about how changes in proteinuria and kidney function early in disease course are associated with long-term risk of KF. This is particularly important in understanding how short-term results from clinical trials might translate into longer-term outcomes. We used data from 371 UK patients with C3G and IC-MPGN recruited to the National Registry of Rare Kidney Diseases (RaDaR) to investigate associations between change in proteinuria and estimated glomerular filtration rate (eGFR) slope from diagnosis to 6, 12, and 24 months and KF. Median follow-up time was 11.0 years, during which 40% of patients reached KF. We found that while 2-year eGFR slope had a modest association with KF, decrease in urinary protein levels (urine protein-creatinine ratio [UPCR]) between diagnosis and 12 months was strongly associated with lower KF risk. Those with a UPCR <100 mg/mmol at 12 months had a 90% reduction in their risk of KF.

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Received 2 October 2024; revised 28 April 2025; accepted 6 June 2025

C3 glomerulopathy (C3G) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN) are rare kidney disorders in which there is glomerular inflammation, increased mesangial matrix and cellularity, capillary wall thickening with deposition of immunoglobulins (in IC-MPGN) and/or complement C3 (seen in both C3G and IC-MPGN). C3G is further subdivided into C3 glomerulonephritis and dense deposit disease (DDD) based on electron micrographic appearances. Presentation typically includes proteinuria and/or other features of kidney disease such as hematuria, hypertension, or renal impairment. These conditions have a combined incidence of 3-5 per million population.[1,2] Although the biopsy features of C3G and IC-MPGN can also be seen in disorders in which there is sustained activation of the immune system (such as persistent infection or autoimmune disease) the diagnosis of primary MPGN in the UK is reserved for those cases in which an underlying cause of immune activation is not identified. Although in most cases the cause of C3G and IC-MPGN is unknown, abnormal activation of the complement alternative pathway is frequently present in both disease categories. This can be attributed to the development of autoantibodies, most commonly C3 nephritic factor or, less often, can be associated with Mendelian[3–9] or non-Mendelian rare or common genetic variants[10–14] affecting innate or adaptive immunity; with comparable prevalence of variants and autoantibodies reported in both disorders.[11,15,16] Together with the presence of C3 deposited in the kidneys in almost all cases and the frequent serological evidence of C3 consumption,[10,11,15,17] these data have provided a compelling rationale for therapeutic targeting of the complement system in these disorders.

While the clinical presentation and diagnosis of these disorders are well-established, long-term outcomes and prognostic features are less well understood, with the literature dominated by single-center series, or studies with limited follow-up, focusing on baseline predictors of disease progression and prone to ascertainment bias. Nonetheless, prognostic markers such as estimated glomerular filtration rate (eGFR), hypoalbuminemia, and biopsy findings of interstitial fibrosis and tubular atrophy, crescents, and segmental sclerosis[11,18–24] have been consistently shown to be associated with kidney failure (KF) in both adult and pediatric IC-MPGN and/or C3G cohorts.[12,19–25] Literature regarding baseline proteinuria is more conflicting: in a study of 156 patients with C3G or IC-MPGN, baseline proteinuria >2 g/d was independently associated with the composite outcome of doubling of serum creatinine or KF.[20] However, in a cohort of 111 patients with C3G from the United States and 164 from France, the association of baseline proteinuria with KF was nonsignificant in the multivariable model.[18,25] Finally, the GLOSEN investigators demonstrated a ≥50% decrease in proteinuria over follow-up or within 6-12 months to be associated with a slower eGFR decline and lower risk of KF.[26,27]

While case series and small observational studies have suggested a potential benefit of corticosteroids and mycophenolate, response to treatment varies, and long-term outcomes remain poor. The nephrology community therefore awaits the results of several complement inhibition randomized trials. However, interpreting the potential clinical impact of an intervention for rare kidney diseases based on evidence of efficacy in a short (i.e., 0.5–2 year) clinical trial is often hampered by lack of direct data demonstrating efficacy in reducing the key clinically relevant outcome of KF. Thus, data are needed inform appraisal of the likely clinical impact of early surrogate endpoints (such as proteinuria and short-term changes in eGFR), amenable to study in relatively short duration trials with limited numbers of participants, on long-term outcomes such as KF. There is growing interest in the extent to which these endpoints can serve as reliable surrogates for hard kidney outcomes and thus inform regulatory decisions and health care planning.[28–30]

Both observational data and meta-analyses of controlled trial treatment effects have supported the use of eGFR slope,[31–33] proteinuria in the context of chronic kidney disease (CKD),[34] and IgA nephropathy.[35,36] Subsequently, IgA nephropathy therapies that demonstrate a short-term reduction in proteinuria in clinical trials can now apply for accelerated approval by the US Federal Drug Administration with full approval granted following confirmation that the drug slows disease progression as measured by eGFR decline over 24 months.

To address this unmet need in C3G and IC-MPGN, we analyzed longitudinal data from 371 incident patients enrolled in the UK National Registry of Rare Kidney Diseases (RaDaR) to quantify the relationships between early changes in proteinuria and eGFR with the clinically important outcome of KF long term. This study addresses and quantifies Prentice's[37] first tenet for surrogate endpoints: that a surrogate endpoint should have a strong association with a true outcome. The subsequent tenet—that treatment effect on the surrogate must capture the treatment effect on the clinical outcome—is best achieved through meta-analysis of controlled trials and is beyond the scope of this study.[33,38] Additionally, while medication data enrichment within RaDaR is ongoing, current data limitations preclude robust analyses of therapies patients have been exposed to historically.

METHODS

Data source

RaDaR recruits patients from 108 National Health Service (NHS) sites with both retrospective and prospective data collection through linkage with hospital laboratories for routine blood and urine test results via the UK Renal Data Collaboration, and with the UK Renal Registry (UKRR) for validated data on initiation of kidney replacement therapy (KRT), including data provided by NHS Blood and Transplant. Patients provide written informed consent at

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recruitment. Details of recruitment characteristics and potential biases have been reported previously.[39]

Inclusion and exclusion criteria for RaDaR are detailed in the Supplementary Methods.

Study population

Data from all prevalent patients recruited to RaDaR with 1 of the above conditions and diagnosed between January 2000 (when proteinuria reporting to RaDaR was established) and December 2022 were extracted on February 13, 2025. Participants with an eGFR <15 ml/min per 1.73 m^2 or receiving KRT at diagnosis were excluded.

Patients who could be reliably classified as either C3G (n = 203) or IC-MPGN (n = 168) by updated (post-2012) criteria[40] were included. Any patients in whom classification by updated criteria was unclear were grouped as "primary MPGN—not otherwise specified" (primary MPGN-NOS); and their data are presented in the Supplementary Methods. Diagnoses were established by review of histopathological and clinical records (detailed in Figure 1[13,19] and the Supplementary Methods).

All patients classified as either C3G or IC-MPGN had data linkage with the UKRR for data on KRT initiation and death.

A subset of these patients also had eGFR and proteinuria measurements available at diagnosis and at 12 months post diagnosis, which enabled analyses investigating the association between proteinuria, eGFR changes, and KF in this group.

Variable and outcome definitions

Baseline or diagnosis date was defined by kidney biopsy date or in the absence of this, date of diagnosis recorded in RaDaR. Time of diagnosis window was defined as ±3 months from diagnosis date. eGFR was calculated from plasma creatinine results using equations from the Chronic Kidney Disease Epidemiology Collaboration (2009) without race adjustment or Schwartz equation for those ≤16 years.[41,42] KF was defined as dependance on KRT or eGFR ≤15 ml/min per 1.73 m^2 maintained for at least 4 weeks.[43] Follow-up time was defined as time between date of diagnosis and last available test result, or whichever occurred first, KF or death from any cause.

Statistical analyses

Categorical data were reported as frequencies (percentages) and medians (interquartile range [IQR]) for nonnormally distributed continuous data. Kaplan-Meier analyses were used to compare time to KF for C3G and IC-MPGN. Univariable Cox modeling was used to identify risk factors associated with KF for each disease group. Variables specified *a priori* included age, sex, CKD stage, complement C3 and C4, random urine protein-creatinine ratio (UPCR) at diagnosis and at 12 months, immunosuppression within first year of diagnosis. Variables achieving a significance threshold of $P < 0.05$ were included in the multivariable model. A 2-sided *P*-value of 0.05 was considered significant. To examine the association between UPCR and time to KF, Cox regression was used to investigate UPCR values, percentage change, and absolute reduction at different time points (diagnosis, 6 months, and 12 months), adjusted for sex, age, UPCR, and eGFR at diagnosis. A reduction of 50 mg/mmol (0.44 g/g) is presented to examine the lowest prognostically meaningful change in UPCR. UPCR values at 12 months were examined in 2 ways: (i) comparing individuals achieving a UPCR <100 mg/mmol and 100–300 mg/mmol with a reference group of those >300 mg/mmol; (ii) Comparing patients with UPCR <100 mg/mmol with those ≥100 mg/mmol, and then repeating, using thresholds of 200 and 300 mg/mmol to dichotomize the patients. Inception time for the Cox model was diagnosis date, and patients were censored at death.

Annualized rate of eGFR loss (eGFR slope) was calculated over full duration of follow-up, comparing C3G and IC-MPGN groups, and for the first 2 years following diagnosis. A linear mixed model with random intercept and random slope was used to estimate each patient's eGFR slope. Patients were required to have at least 4 eGFR measurements for inclusion. The association of KF with eGFR slope over 2 years and with percentage change in eGFR at 2 years (sustained over a minimum of 90 days) was also investigated, adjusting for age, sex, and eGFR at diagnosis. Finally, the impact of eGFR variability on KF, as measured using the coefficient of variation and average real variability, was evaluated using Cox regression and adjusted for the same covariates.

A joint model was used to investigate the association of longitudinal UPCR during follow-up and KF and was stratified by diagnosis group (details included in the Supplementary Materials).

Data availability for each variable is shown in Supplementary Table S1. The analyses were restricted to patients with complete data required for each calculation; multiple imputation has not been performed. Percentages and proportions are of those with data available.

Analyses were performed using SAS v9.4 (SAS Institute), STATA v16.1 (IBM Corp.), and R v4.3.3 (R Foundation).

Ethics

This report adheres to the Strengthening the Reporting of Observation Studies in Epidemiology statement. RaDaR has ethical approval as a research registry provided by NHS South-West Central Bristol Research ethics committee (14/SW/1088) and by the RaDaR and UKRR operational committees.

RESULTS

Demographics and baseline characteristics

We included 371 patients, 203 (55%) with C3G and 168 (45%) with IC-MPGN. Of the patients with C3G, 138 (68%) had C3 glomerulonephritis (C3GN) subtype, and 65 (32%) DDD subtype (Table 1). For 352 patients it was not possible to confirm a diagnosis of C3G or IC-MPGN; results for these patients (primary MPGN-NOS) are presented in Supplementary Table S2. The median age at diagnosis for patients with C3G was 20 years (IQR: 11–40) and 25 years

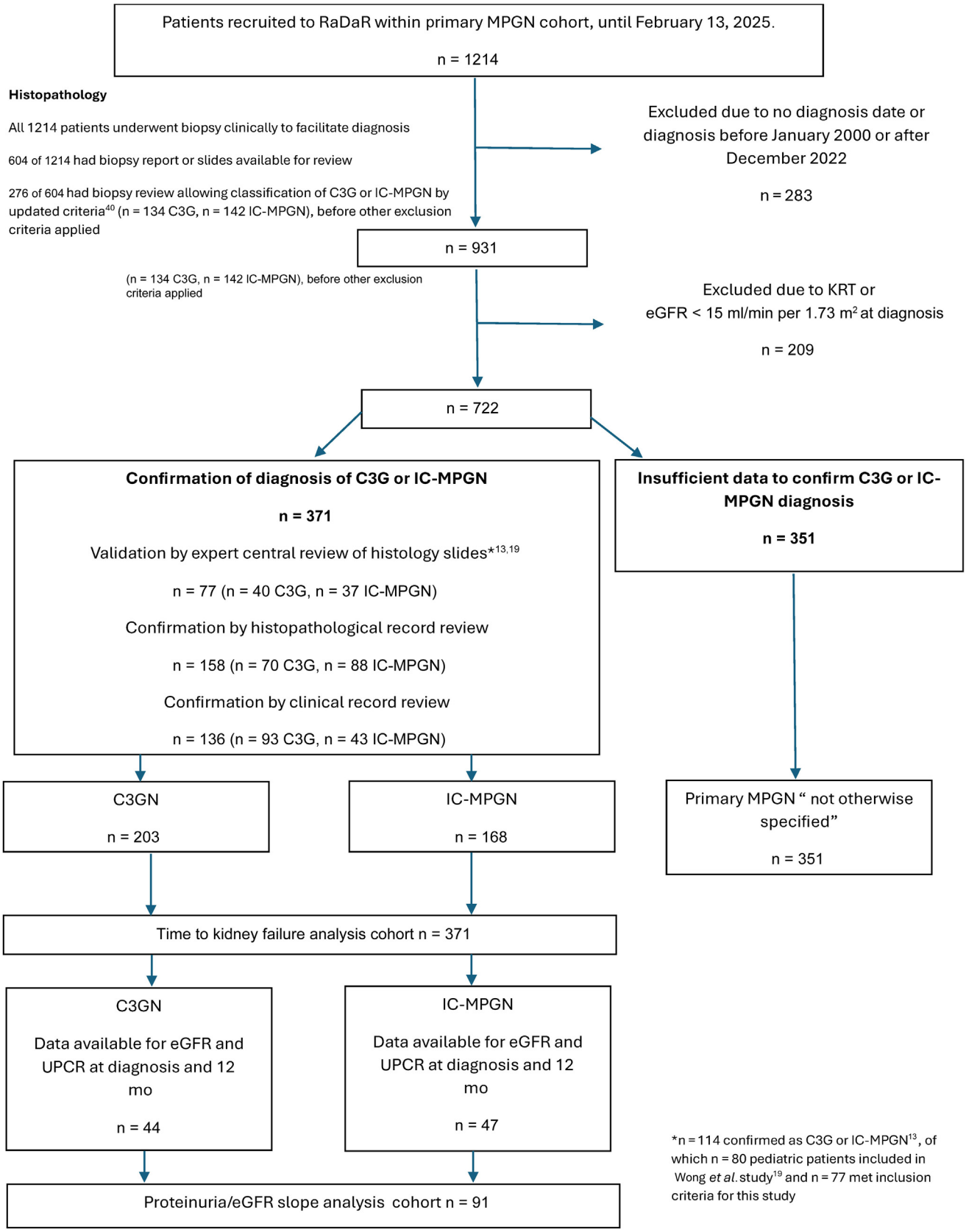

Figure 1 | Study flow diagram and inclusion and exclusion criteria. C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; KRT, kidney replacement therapy; MPGN, membranoproliferative glomerulonephritis; RaDaR, National Registry of Rare Kidney Diseases. Q23

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Table 1 | Baseline demographics and outcomes

	C3G					
	C3GN		DDD		IC-MPGN	
	N = 138	(%)	N = 65	(%)	N = 168	(%)
Age at diagnosis, yr, n	138		65		168	
Median (IQR)	24 (14–46)		14 (10–34)		25 (10–54)	
Pediatric (<18 yr)	50	(36)	41	(63)	73	(43)
Sex, n	138		65		168	
Female	54	(39)	31	(48)	81	(48)
Ethnicity, n	126		58		157	
White	113	(90)	47	(81)	139	(89)
Median follow up duration, n	138		65		168	
Median (IQR), yr	10.6 (9.4–11.2)		10.6 (8.9–18.0)		12.0 (7.5–15.6)	
Serum albumin at diagnosis, n	60		38		92	
Mean (SD), g/l	32 (10)		29 (8)		28 (8)	
Complement C3 levels at diagnosis, n	48		27		45	
Median (IQR), g/l	0.41 (0.20–1.01)		0.36 (0.12–0.73)		0.64 (0.17–0.94)	
Complement C4 levels at diagnosis, n	48		26		44	
Median (IQR), g/l	0.25 (0.16–0.33)		0.22 (0.15–0.31)		0.14 (0.09–0.25)	
Kidney failure event, n	138		65		168	
Yes	57	(41)	29	(45)	62	(37)
Immunosuppression within 1 yr of diagnosis, n	110		53		129	
Yes	42	(38)	22	(42)	63	(49)
RAS inhibitor within 1 yr of diagnosis, n	110		53		129	
Yes	44	(40)	23	(43)	54	(42)

	eGFR and proteinuria analysis population	
	C3G (C3GN/DDD)	IC-MPGN
	N = 44	N = 47
UPCR, mg/mmol, median (IQR)		
Diagnosis	532 (301–915)	581 (310–847)
6 mo	148 (81–312)	130 (44–295)
12 mo	117 (55–321)	102 (25–360)
eGFR at diagnosis, ml/min per 1.73 m^2		
Median (IQR)	70 (40–94)	73 (41–114)

C3GN, C3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IQR, interquartile range; RAS, renal angiotensin system; UPCR, urine protein creatinine ratio.
Percentages are proportions of those with data available.

(IQR: 10–54) for those with IC-MPGN. Patients with DDD subtype had a younger median age at diagnosis than those with C3GN (14 [IQR: 10-34] years vs. 24 [IQR: 14–46] years, respectively), and a higher percentage of patients diagnosed at <18 years old compared to patients with C3GN or IC-MPGN.

Approximately one-half of all participants were female (166 of 371, 45%); this proportion was lower in the C3GN subgroup (54 of 138, 39%). Median C3 levels at diagnosis were lowest in the DDD subgroup (0.36 [IQR: 0.12–0.73] g/l), and median C4 levels lowest in patients with IC-MPGN (0.14 [IQR: 0.09-0.25] g/l).

At least 1 medication entry was available for 292 of 371 participants within the first year of diagnosis (Supplementary Table S1). Of those with data, 127 of 292 (43%) received at least 1 immunosuppressant and 119 of 292 (41%) received corticosteroids alone or as combination therapy. Within 1 year of diagnosis, 121 of 292 participants (41%) were recorded as receiving a renal-angiotensin system inhibitor, but this could reflect incomplete medication data collection.

Kidney replacement therapy

Over the course of follow-up, 86 of 203 participants (42%) with C3G and 62 of 168 (37%) with IC-MPGN experienced a KF event. Most had started KRT at time of analyses: 83 of 86 (97%) with C3G and 59 of 62 (95%) with IC-MPGN; however, there were 2 deaths prior to KRT initiation.

Of those reaching KF, 27 of 86 (31%) with C3G and 14 of 62 (23%) with IC-MPGN were diagnosed in childhood (<18 years). Most patients with C3G began KRT on maintenance hemodialysis (47 of 83 [57%]), followed by 21 of 86 (24%) on peritoneal dialysis, and 15 of 86 (17%) received a preemptive kidney transplant. Proportions of patients starting on each modality were similar for IC-MPGN: hemodialysis, 32 of 59

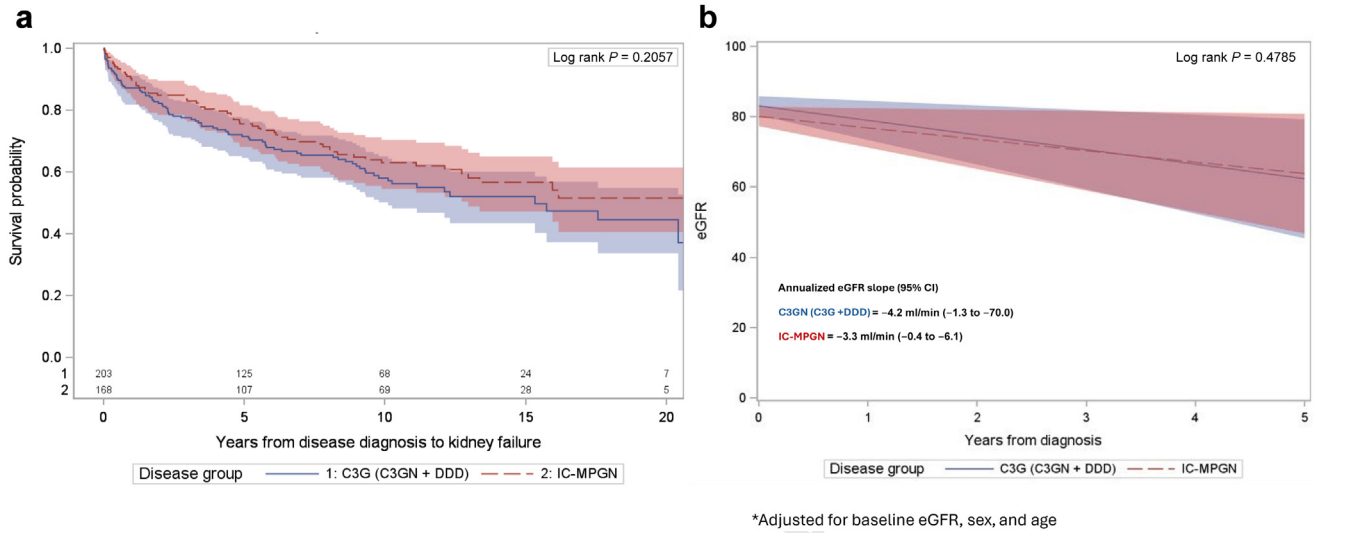


Figure 2 | Kaplan-Meier curves of time to kidney failure by disease subgroup (a). Adjusted estimated glomerular filtration rate (eGFR) slope over full duration of follow-up truncated at 5 years by disease subgroup (**b**). C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; MPGN, membranoproliferative glomerulonephritis. Q28

(54%); peritoneal dialysis, 17 of 59 (29%); preemptive transplantation, 10 of 59 (17%). For those diagnosed in childhood, rates of preemptive transplantation were slightly higher: 5 of 27 (19%) for C3G and 4 of 14 (29%) for IC-MPGN.

Over the follow-up period, 60 of 86 patients (70%) with C3G and 40 of 62 (65%) with IC-MPGN who reached KF underwent at least 1 kidney transplant. The 5-year graft survival was 73% (95% confidence interval [CI]: 57%–83%) for C3G, 71% for IC-MPGN and 75% (95% CI: 67%–82%) for both groups combined (Supplementary Figure S1). The 25th centile time to graft failure for all subsequent transplants for C3G and IC-MPGN combined was 3.3 years (95% CI: 0.7–3.6 years).

Risk factors for progression to KF

Linear mixed models of eGFR slope over full duration of follow-up, and Kaplan-Meier analyses demonstrated no statistically significant difference in progression to KF between patients with C3G and IC-MPGN (Figure 2).

Risk factors associated with progression to KF were investigated using univariable and multivariable models (Table 2). In the univariable models, age, CKD stage at diagnosis and UPCR levels at 12 months were independently associated with KF for both C3G and IC-MPGN, whereas UPCR levels at diagnosis, albumin, immunosuppression use within 1 year, and complement C3 and C4 at diagnosis were not. In the multivariable models, female sex and lower CKD stage at diagnosis were associated with a lower hazard of KF for both C3G and IC-MPGN groups. UPCR <100 mg/mmol at 12 months was associated with a decreased hazard of KF for C3G, and there were no KF events in the <100 mg/mmol group for IC-MPGN. Results were similar for patients with primary MPGN-NOS (Supplementary Table S3).

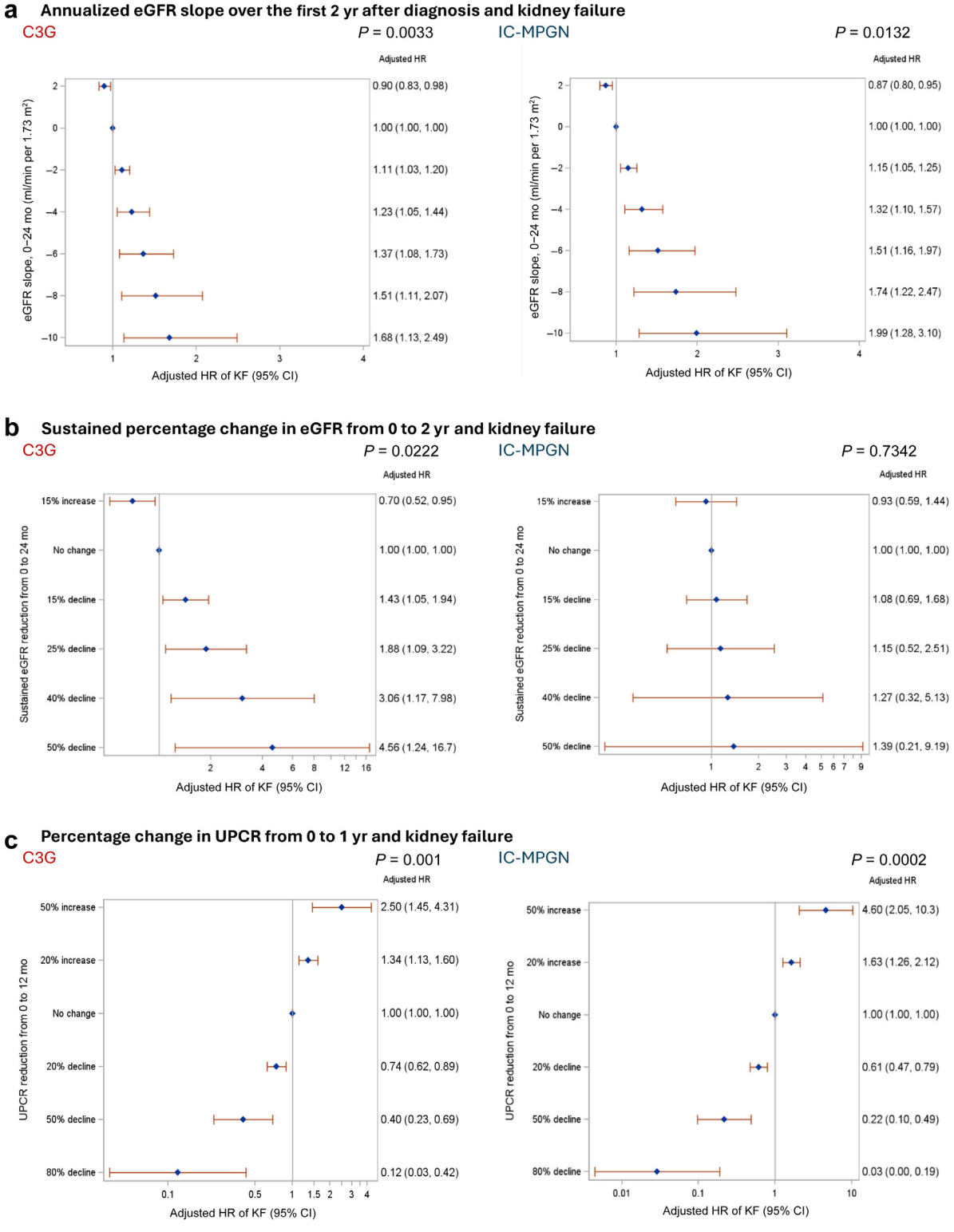
To address whether changes in eGFR and proteinuria early in disease course are associated with long-term development of KF, we used a subset of 91 patients for whom data on UPCR and eGFR at diagnosis and 1-year post diagnosis were available (C3G, n = 44; IC-MPGN, n = 47) (Table 1, Figure 1). Baseline characteristics of this subset of patients and the overall cohort were generally comparable (Supplementary Table S4), although the restricted cohort were younger and had higher recorded immunosuppression and renal angiotensin system inhibitor use at 1 year. All subsequent analyses were performed on this subset of patients.

We first demonstrated that annualized eGFR slope calculated over the first 2 years following diagnosis was strongly associated with KF (C3G, $P = 0.0033$; IC-MPGN, $P = 0.0132$) (Figure 3a). However, an annual decline of 10 ml/min per 1.73 m^2 over the first 2 years was associated with only a modest increase in KF hazard for both C3G (hazard ratio [HR]: 1.68; 95% CI: 1.13–2.49) and IC-MPGN (HR: 1.99; 95% CI: 1.28–3.10). As a sensitivity analysis, those with an eGFR >60 ml/min per 1.73 m^2 at diagnosis were excluded, and subsequent point estimates were only marginally higher (Supplementary Figure S2). Replicating this in a prevalent cohort (diagnosed >1 year prior to inclusion) resulted in higher point estimates (Supplementary Figure S3). Results for sustained percentage change in eGFR at 2 years were more conflicting; percentage change in eGFR was associated with KF for C3G ($P = 0.0022$), but not IC-MPGN ($P = 0.7342$) (Figure 3b) or for both groups combined ($P = 0.1210$) (Supplementary Figure S4). The distribution of participants' eGFR changes is available in Supplementary Figure S5. eGFR variability as measured by both coefficient of variation and average real variability was not associated with KF (Supplementary Figures S6 and S7).

Table 2 | Univariable and multivariable cox model of time to kidney failure according to baseline characteristics for C3G and IC-MPGN Q25

	C3G				IC-MPGN			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at diagnosis, per 10 yr	1.25 (1.12–1.38)	<0.0001	1.10 (0.98–1.24)	0.1001	1.22 (1.1–1.35)	0.0002	1.15 (1.02–1.30)	0.0239
Female	0.55 (0.35–0.86)	0.0087	0.54 (0.34–0.85)	0.0084	0.67 (0.4–1.11)	0.1185	0.56 (0.33–0.96)	0.0358
CKD stage at diagnosis								
1 and 2	Ref		Ref		Ref			
3	2.42 (1.19–4.93)	0.0151	1.67 (0.79–3.55)	0.1810	2.67 (1.22–5.8)	0.0141	1.69 (0.75–3.82)	0.2066
4	16.02 (7.85–32.68)	<0.0001	12.63 (5.82–27.41)	<0.0001	6.79 (2.69–17.11)	<0.0001	3.56 (1.26–10.01)	0.0163
Albumin, g/l								
<30	Ref				Ref			
≥30	0.71 (0.35–1.43)	0.3370			0.93 (0.44–1.97)	0.8541		
Complement C3 g/l	1.01 (0.99–1.02)	0.3476			0.96 (0.75–1.22)	0.7129		
Complement C4 g/l	1.03 (0.99–1.08)	0.1669			0.87 (0.48–1.58)	0.6380		
UPCR at diagnosis, mg/mmol								
>300	Ref				Ref			
100–300	0.45 (0.19–1.06)	0.0678			0.51 (0.18–1.48)	0.2154		
<100	0.36 (0.13–1.00)	0.0495			0.33 (0.04–2.42)	0.2746		
UPCR at 12 mo, mg/mmol								
>300	Ref				Ref			
100–300	0.69 (0.29–1.68)	0.4168	0.85 (0.34–2.12)	0.7220	0.47 (0.15–1.44)	0.1837	0.34 (0.11–1.06)	0.0623
<100	0.18 (0.06–0.49)	0.0010	0.21 (0.073–0.596)	0.0035	NE		NE	
Immunosuppression in year 1	1.23 (0.64–2.35)	0.5292			0.66 (0.29–1.48)	0.3120		

C3G, C3 glomerulopathy; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; NE, no events; Ref, reference; UPCR, urine protein-creatinine ratio.
Patients were censored at death. Q26



*Adjusted for age, sex, and eGFR at diagnosis

Figure 3 | (a–c) Forest plots of urine protein-creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) changes within 2 years of diagnosis and hazard ratio of kidney failure (KF) for C3 glomerulopathy (C3) glomerulonephritis (C3GN) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN). CI, confidence interval.

Table 3 | UPCR thresholds and changes in UPCR in the first 12 months following diagnosis and risk of kidney failure for C3G and IC-MPGN

UPCR thresholds at 12 months and HR (95% CI) of kidney failure			50% decline in UPCR and HR (95% CI) of kidney failure[a]				50 mg/mmol decline in UPCR and HR (95% CI) of kidney failure[a]			
UPCR threshold[b]	Adjusted HR[c]	*P* value	Time point from	Time point to	Adjusted HR[d]	*P* value	Time point from	Time point to	Adjusted HR[d]	*P* value
C3G (C3GN and DDD), N = 44										
<100 mg/mmol	0.18 (0.05–0.65)	0.0086	Diagnosis	6 mo	0.61 (0.35–1.08)	0.0898	Diagnosis	6 mo	0.87 (0.65–1.18)	0.3767
<200 mg/mmol	0.13 (0.04–0.43)	0.0009	Diagnosis	1 yr	0.4 (0.23–0.69)	0.0010	Diagnosis	1 yr	0.62 (0.43–0.91)	0.0136
<300 mg/mmol	0.26 (0.1–0.67)	0.0054	6 mo	1 yr	0.33 (0.14–0.76)	0.0097	6 mo	1 yr	0.71 (0.51–1.00)	0.0435
IC-MPGN, N = 47										
<100 mg/mmol	NE	NE	Diagnosis	6 mo	0.66 (0.42–1.04)	0.0698	Diagnosis	6 mo	0.72 (0.51–1.01)	0.0597
<200 mg/mmol	0.03 (0.004–0.25)	0.0011	Diagnosis	1 yr	0.22 (0.1–0.49)	0.0002	Diagnosis	1 yr	0.52 (0.35–0.79)	0.0018
<300 mg/mmol	0.04 (0.01–0.24)	0.0004	6 mo	1 yr	0.12 (0.03–0.58)	0.0079	6 mo	1 yr	0.062 (0.008–0.50)	0.009
Combined cohort (C3G and IC-MPGN), N = 91										
<100 mg/mmol	0.10 (0.03–0.30)	<0.0001	Diagnosis	6 mo	0.62 (0.44–0.86)	0.0048	Diagnosis	6 mo	0.79 (0.65–0.96)	0.0183
<200 mg/mmol	0.13 (0.06–0.31)	<0.0001	Diagnosis	1 yr	0.40 (0.28–0.56)	<0.0001	Diagnosis	1 yr	0.63 (0.50–0.78)	<0.0001
<300 mg/mmol	0.15 (0.07–0.34)	<0.0001	6 mo	1 yr	0.26 (0.13–0.50)	<0.0001	6 mo	1 yr	0.63 (0.48–0.82)	0.0007

C3G, C3 glomerulopathy; C3GN, C3 glomerulonephritis; CI, confidence interval; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; NE, not estimable; UPCR, urine protein-creatinine ratio.
[a]Analyses exclude those with UPCR <50 mg/mmol at diagnosis.
[b]Comparison of patients who do and do not reach each threshold.
[c]Adjusted for age, sex, and eGFR.
[d]Adjusted for eGFR, age, sex, and baseline UPCR.

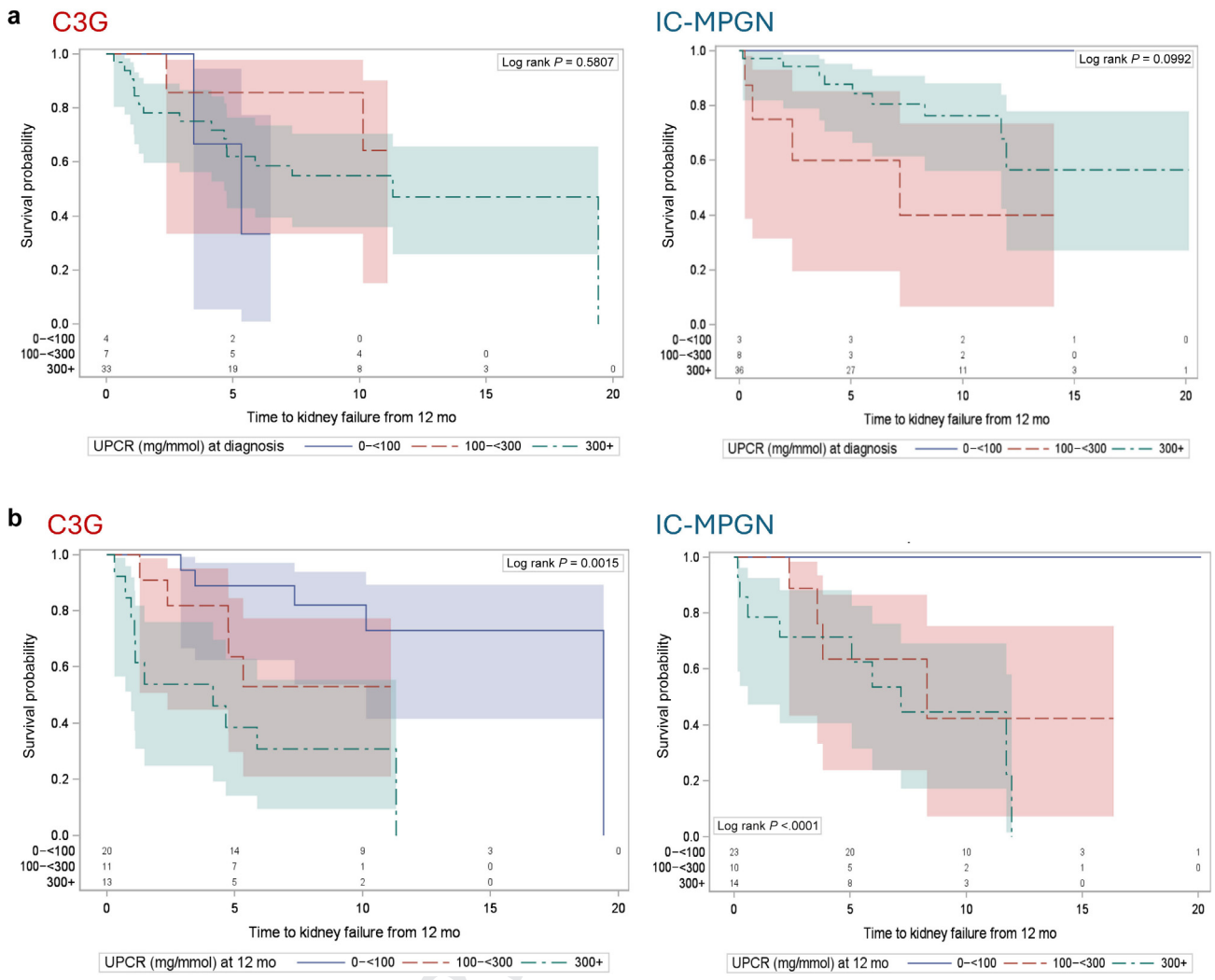


Figure 4| Kaplan-Meier curves of time to kidney failure according to urine protein-creatinine ratio (UPCR) category at diagnosis (a) and 12 months (b), for C3 glomerulopathy (C3G) and immune-complex membranoproliferative glomerulonephritis (IC-MPGN).

Next, we examined changes in UPCR across diagnosis, 6-month, and 12-month time points as may be presented in a clinical trial, excluding those with a UPCR <50 mg/mmol at diagnosis. As outlined, the objective was to quantify the KF hazard associated with increases and decreases in UPCR, regardless of why these may have occurred. The distribution of UPCR measurements in both the C3G and IC-MPGN cohorts across different time points can be found in Supplementary Figure S8, with a median UPCR of 532 (IQR: 301–915) mg/mmol at diagnosis and 117 (IQR: 55–321) mg/mmol at 12 months for C3G and median UPCR of 581 (IQR: 310–847) mg/mmol at diagnosis and 102 (IQR: 25–360) mg/mmol at 12 months for IC-MPGN. Absolute reduction of UPCR between 0 and 12 months was significantly associated with lower risk of KF for both patients with C3G and those with IC-MPGN (Table 3); a 50-mg/mmol decline was estimated to have an adjusted HR of 0.63 (95% CI: 0.50–0.78) for the combined cohort. Additionally, while a 50% reduction in UPCR at 6 months did not reach statistical significance for either group, a halving of UPCR from diagnosis to 12 months and 6 to 12 months was strongly associated with a lower rate of KF for both patients with C3G (0–12 months, HR: 0.40; 95% CI: 0.23–0.69; $P = 0.001$; 6–12 months, HR: 0.33; 95% CI: 0.140.76; $P = 0.0097$) and patients with IC-MPGN (0–12 months, HR: 0.22; 95% CI: 0.1–0.49; $P = 0.0002$; 6–12 months, HR: 0.12; 95% CI: 0.03–0.58; $P = 0.0079$). Forest plots demonstrating how this risk varies for a range of UPCR changes from diagnosis to 12 months are presented in Figure 3c with the distribution of UPCR changes in our cohort presented in Supplementary Figure S9.

From both a clinical practice and trial perspective, understanding the extent to which reaching certain thresholds diminishes KF risk can often be useful. Figure 4 shows time to KF according to UPCR category for C3G and IC-MPGN. Table 3 shows the KF hazard for those who reach a specific threshold of UPCR at 12 months, compared to those who do not reach that threshold, for the combined cohort and each group separately. For example, reaching a UPCR of <100 mg/

mmol at 12 months was associated with a 90% lower rate of KF compared to patients achieving a UPCR >100 mg/mmol, for C3G and IC-MPGN combined (Table 3). While reaching a UPCR of <200 mg/mmol and <300 mg/mmol at 12 months also showed similarly large reductions in the hazard of KF, this is likely due to inclusion of patients achieving a UPCR <100 mg/mmol in those groups; when comparing patients reaching a UPCR of 100–300 mg/mmol to a reference group of >300 mg/mmol, we found no statistically significant reduction in KF risk at these thresholds (Table 2).

To verify this finding was not driven by inclusion of low-risk participants whose UPCR started and remained low, we performed a sensitivity analysis excluding those with a UPCR <100 mg/mmol at diagnosis (Supplementary Table S5), which showed similar results. Results were comparable in the MPGN-NOS cohort (Supplementary Table S6).

Joint models showed a significant association of UPCR during total follow-up with KF, adjusting for age, sex, and eGFR at diagnosis (Supplementary Table S7). Adjusted HRs for a halving of UPCR were 0.24 (95% CI: 0.10–0.56) for C3G and 0.54 (95% CI: 0.36–0.80) for IC-MPGN.

DISCUSSION

We present long-term longitudinal data from 371 patients with C3G or IC-MPGN within RaDaR. Using an incident cohort, we provide valuable insights into the natural history of these ultra-rare disorders, expanding on small-scale observational studies[9,18,20,26] and providing quantitative estimates for the relationship of early surrogate endpoints on KF hazard. We present analyses of C3G and IC-MPGN combined and separately for reference, given evidence of overlapping pathogenesis, specifically complement pathway dysregulation and thus suitability for inclusion in targeted therapy trials.[10,11] A particular strength of this study is the median follow-up 11.0 (IQR: 7.4–15.1) years, during which 40% of participants reached KF, illustrating the significant unmet need for effective treatments in these disorders.[44] Recent results from the GLOSEN registry showed similarly high rates of KF (70% kidney survival over a median follow-up of 5.4 years, compared to 73% 5-year kidney survival [95% CI: 68%−78%] in this cohort), despite significantly higher rates of corticosteroid use (84%−90% compared to 38%−49% in this cohort), perhaps suggesting limited effectiveness of current treatments. This is notably compounded by a reduced 5-year first allograft survival of 75% compared with 84%−87% 5-year graft survival for all (adult or pediatric) deceased donor recipients in the United Kingdom,[45,46] and evidence that fewer pediatric patients achieve the optimal treatment of preemptive transplantation (22%) compared to >30% of the overall incident UK pediatric KRT population,[47] although this proportion can be as low as 3% for some glomerular diseases.

In a multivariable Cox regression model, female sex was associated with lower risk of KF for both disease groups. These differences are not explained by earlier ascertainment: while females had a younger median age at diagnosis (females, 18 [IQR: 10–49] years; males, 24 [IQR: 12–46] years; $P = 0.27$), and better baseline kidney function (median eGFR at diagnosis: females, 66 [IQR: 39–99] ml/min per 1.73 m^2; males, 64 [IQR:40–104] ml/min per 1.73 m^2; $P = 0.80$), these differences did not reach statistical significance. To our knowledge, this is the first study to describe sex differences in kidney outcomes in C3G and IC-MPGN, and verification in other cohorts would be beneficial.

Consistent with previous studies,[11,48] we show no significant difference in time to KF between patients with C3G and those with IC-MPGN nor in mean eGFR slope over the first 5 years of follow-up and that eGFR and proteinuria are strongly associated with long-term outcomes in both groups.[19,22] However, our analysis showed stronger relationships of these parameters at 6–24 months with long-term risk of KF, with the association of proteinuria (and changes in proteinuria) particularly significant. Addressing the utility of these endpoints in a disease-specific context, we show that while eGFR slope early in disease course is strongly associated with KF, the magnitude of the effect is relatively modest, even over 2 years, compared to change in proteinuria over 1 year. This remains the case irrespective of whether baseline eGFR is above or below 60 ml/min per 1.73 m^2 as has also been shown using CKD data,[31] although the effect of eGFR slope on KF was more marked in a prevalent cohort (Supplementary Figure S3). This suggests that eGFR slope has more limited predictive power for C3G and IC-MPGN compared to other kidney disorders, particularly early in the disease.

As previously reported,[19,26] proteinuria at baseline was not associated with KF, whereas proteinuria reduction at 12 months was. This complements previous reports from the GLOSEN registry, which showed a ≥50% reduction in proteinuria at 12 months was associated with a lower risk of KF (HR: 0.83; 95% CI: 0.69–0.95).[26] We further demonstrate the novel finding that smaller reductions in proteinuria as little as 50 mg/mmol at 12 months were statistically significantly associated with lower risk of KF, as was a percentage decrease in UPCR as little as 20%, although most patients in the cohort had larger changes in proteinuria (Supplementary Figure S9).[27] By determining how KF risk changes across a range of absolute and percentage decreases in proteinuria, even for reductions smaller than the ≥50% decrease shown in previous studies,[27] our results help enable more accurate prognostication clinically and more comprehensive appraisal of clinical trial results.

Achieving a threshold UPCR of <100 mg/mmol by 12 months was particularly strongly associated with lower rate of KF events (HR: 0.10; 95% CI: 0.03–0.30; $P < 0.0001$). Therefore, if proteinuria is shown in clinical trials to be reduced to similarly low levels by therapies that act by reducing disease activity as compared to standard of care, it is logical to infer that long-term KF hazard will be similarly reduced, potentially supporting the use of this accessible endpoint in future trials as a surrogate for KF. However, the thresholds used in our study are currently demonstrative, and validation in other cohorts are needed before use as clinical trial endpoints or treatment targets.

Our findings must be considered in the context of the limitations inherent in registry studies including incomplete data. The latter is mitigated through data linkages with UKRR and NHS Blood and Transplant that provide validated long-term KF endpoints for all UK patients as well as increasing prospective data collection via automated laboratory feeds from NHS hospitals. However, this remains a real-world dataset in which standard of care may impact the availability of eGFR and UPCR data at time points, as may patient or disease characteristics. It is most representative of the population and clinical practice patterns in the United Kingdom, which may be different in other settings. We have presented analyses examining the association between eGFR and UPCR changes early in disease and KF using a restricted cohort with data available at all requisite time points. This cohort was younger at diagnosis and more likely to be recorded as receiving medications in their first-year post diagnosis than those without available data and may therefore represent a population with earlier disease onset and a more intensive standard of care. While our analyses are particularly pertinent to this population, these characteristics should be taken into consideration when interpreting our results.

Additionally, RaDaR does not yet collect data on frailty, which may account for some heterogeneity in data collected across sites, and medication data were limited. The additive prognostic value of autoantibody or genetic variant status could not be assessed with this dataset. Finally, while beyond the scope this study, further work to assess whether treatment effects on intermediate endpoints predict treatment effects on KF may enable upgrade of proteinuria from a "reasonably likely" to a "validated" endpoint as indicated in the biomarkers, endpoints, and other tools resource.[46]

In conclusion, using real-world data from RaDaR, we provide quantitative descriptions of the relationships between early changes in both eGFR and proteinuria, as well as long-term renal outcomes in incident patients with C3G and IC-MPGN. Across a range of measures, we demonstrate that proteinuria a short time after diagnosis is strongly associated with long-term outcomes and notably that UPCR <100 mg/mmol at 1 year is associated with substantially lower risk of KF progression, and that even small reductions in proteinuria could significantly reduce long-term KF risk.

APPENDIX

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DISCLOSURE

CP and NJAW are or were employees and shareholders of Novartis AG, which partially funded the analysis and has applied for marketing authorization for a therapy for C3 glomerulopathy. EKSW declares receiving fees for consulting and presenting from Novartis, Apellis, Alexion, SOBI, Arrowhead, and Biocryst. DPG declares support from St. Peter's Trust for Kidney Bladder and Prostate Research, Novartis AG, Medical Research Council, Kidney Research UK, Kidney Care UK, and Polycystic Kidney Disease Charity (payments to institution); chairs the Rare Diseases Committee of the UKKA; and has received fees for consulting and presenting from Novartis, Alexion, Calliditas, Sanofi, Britannia, SOBI, and Travere. All the other authors declared no competing interests.

DATA STATEMENT

The RaDaR database is hosted by the UK Renal Registry and its metadata are available via https://rarerenal.org. Individual-level data are not available for export. Proposals to perform analyses using the data for academic, audit, or commercial purposes can be made to the RaDaR Operations Group via https://rarerenal.org.

ACKNOWLEDGMENTS

The authors thank all RaDaR participants, their family members, and the UK Renal Registry staff. RaDaR is funded by the UK Kidney Association, UK Medical Research Council, Kidney Research UK, Kidney Care UK, and the Polycystic Kidney Disease Charity.

ROLE OF FUNDERS

CP and NJAW are or were employees and shareholders of Novartis at the time of manuscript submission. Novartis funded part of the research presented here through a research collaboration. The objectives and protocol were developed jointly. The RaDaR team conducted all the analyses and developed the manuscript draft, and all authors discussed the data and provided comments on the manuscript.

FUNDING STATEMENT

RaDaR was originally funded by the Medical Research Council, Kidney Research UK, Kidney Care UK, and the Polycystic Kidney Disease Charity and is now managed and funded by the UK Kidney Association. RaDaR has received ad hoc funding for individual project work and annual funding from various charities to maintain the registry on the National Institute for Health Research portfolio. The analysis for this manuscript was part funded by Novartis AG.

AUTHOR CONTRIBUTIONS

DPG conceived the study and acquired funding. SM, KW, LD, and DP curated data, performed formal analyses, and accessed and verified the data. DPG and SM wrote the initial draft. EKSW, CP, and NJAW assisted with analysis and reviewed and edited the manuscript. DPG and SM had final responsibility to submit for publication.

Supplementary material is available online at www.kidney-international.org.

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