Patient characteristics and renal outcomes of C3G and IC-MPGN in the UK: a retrospective analysis of 287 patients in the UK National Registry of Rare Kidney Diseases (RaDaR)

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RESULTS

Characteristics and clinical outcomes

- 287 patients with biopsy proven C3G or IC-MPGN and a diagnosis date recorded in RaDaR were included. 135 (47%) had confirmed C3G and 152 (53%) IC-MPGN (**Table 1**).
- Median age at diagnosis was 14 years for C3G patients and 23 years for IC-MPGN patients. Most patients in the C3G and IC-MPGN cohorts were white (76% and 81% respectively). 52% of the IC-MPGN cohort and 48% of the C3G cohort were male (**Table 1**).

Time to kidney failure

- Median duration of follow up was 5.8 years for C3G patients (IQR 2.9 – 11.0 years), and 6.8 years for IC-MPGN patients (IQR 1.8 – 11.4 years).
- No significant difference was found in the time from diagnosis to kidney failure for C3G and IC-MPGN patients (median time to kidney failure 9.3 vs 12.0 years respectively, p-value 0.31, **Figure 1**).
- A 20% decrease in UPCR at 1-year post-diagnosis was associated with an increase in 20-year kidney survival (p<0.001, Hazard Ratio 0.651) (**Table 2**) (analyses from C3G and IC-MPGN combined).
- Decrease in UPCR between 6-months and 1-year post-diagnosis also showed a strong association with 20-year kidney survival for both percentage and absolute change in UPCR (p<0.001, Hazard Ratio 0.923 and p<0.001, Hazard Ratio 0.751 respectively) (**Table 2**).

eGFR Slope

- C3G patients had faster annual eGFR decline compared to IC-MPGN patients (4.9 vs 3.3 mL/min/1.73m2/year, **Table 1**).
- Change in UPCR at 6 months post diagnosis was not associated with an increase in annualised eGFR slope for C3G patients (p=0.52) nor for IC-MPGN patients (p=0.70.
- A decrease in UPCR at 1-year post-diagnosis was associated with a decrease in the annualised eGFR slope for C3G patients (p=0.09, slope change=0.07). There was also significant association between UPCR change at 1 year and eGFR slope for IC-MPGN patients (p=0.03, slope change=0.07).

Medications

- Of the 141 patients with medication data, 51 (36%) were adult and 90 (64%) were paediatric at diagnosis. 58% of these patients were given RAS blockade (ACE-I/ARBs), and 46% were given corticosteroids as their initial treatment (**Figure 2**).

Table 1. Characteristics at diagnosis and clinical outcomes

			C3G		IC-MPGN	
			N	%	N	%
Age (years)			**135**	**100**	**152**	**100**
Median (IQR)			14 (9 - 34)		23 (9 - 55)	
Pediatric, n (%)			82	61	71	47
Sex, n (%)			**135**	**100**	**152**	**100**
Male			65	48	79	52
UPCR at diagnosis, n (%)			**62**	**46**	**59**	**39**
Diagnosis	Median (IQR)	mg/mmol	412 (126 - 700)		466 (167 - 820)	
6 months	Median (IQR)	mg/mmol	150 (71 - 436)		92 (28 - 253)	
12 months	Median (IQR)	mg/mmol	128 (25 - 413)		78 (18 - 311)	
eGFR at diagnosis, n (%)			**38**	**28**	**42**	**28**
Median (IQR), mL/min/1.73 m^2			70 (30 - 92)		58 (40 - 110)	
Kidney Failure event, n (%)			**135**	**100**	**152**	**100**
Yes			85	63	107	70
eGFR slope, n (%)			**80**	**60**	**91**	**60**
Mean (95% CI), mL/min/1.73 m^2/year			-4.9 (-7.0, -2.9)		-3.3 (-4.6, -2.1)	

eGFR slope adjusted for UPCR and eGFR at diagnosis

Table 2. Clinical outcomes for patients categorized by change in UPCR and eGFR post-diagnosis (C3G and IC-MPGN combined)

UPCR change			Kidney Failure		
Timepoint from	**Timepoint to**	**Change**	**N**	**HR**	**P-Value**
Diagnosis	6 Month	-20%	65	0.933	0.17
Diagnosis	1 Year	-20%	60	0.651	<0.001
6 month	1 Year	-20%	48	0.923	<0.001
Diagnosis	6 month	-50mg/mmol	55	0.911	0.05
6 month	1 Year	-50mg/mmol	75	0.751	<0.001
eGFR change					
6 month	1 Year	20%	70	0.612	0.07

The hazard ratio is the change in risk of 20-year kidney failure for each associated change in UPCR between diagnosis and 6 months or 1 year, or between 6 months and 1 year post-diagnosis.
Abbreviations: HR, Hazard Ratio; **UPCR**, Urine Protein Creatinine Ratio; **eGFR**, estimated Glomerular Filtration Rate

Figure 1. Kaplan Meier survival curves for patients categorized by disease subgroup

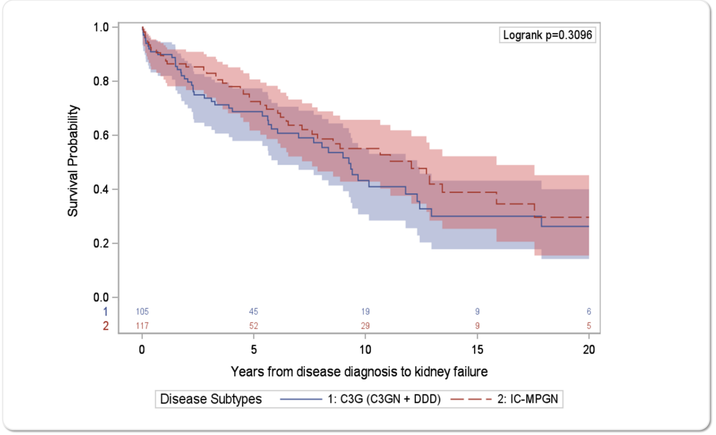
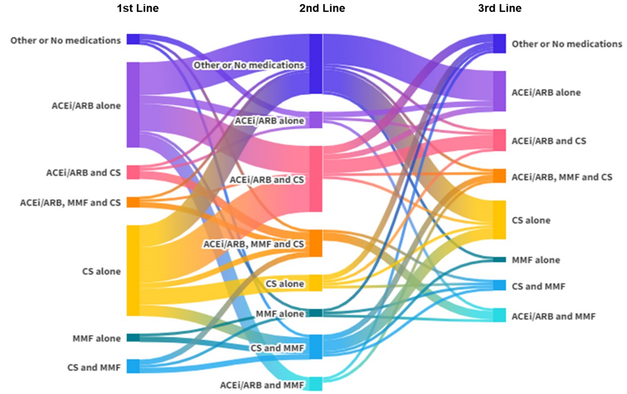


Figure 2. Sankey Plot for patients' medication treatment lines



INTRODUCTION

- Membranoproliferative glomerulonephritis (MPGN) is an ultra-rare chronic kidney disease (CKD).
- MPGN can be further categorized into C3 glomerulopathy (C3G) and immune-complex MPGN (IC-MPGN) based on relative complement and immunoglobulin (Ig) staining on biopsy specimens[1].

Objective

- To describe patients with C3G and IC-MPGN within the UK National Registry of Rare Kidney Diseases (RaDaR) according to their demographic and clinical characteristics, as well as their prescribed treatments and the resulting clinical outcomes.
- To investigate potential biomarkers as predictors for disease progression.

METHODS

Data Source

- This study uses data from the RaDaR database
- Patients with biopsy-proven C3G or IC-MPGN and enrolled into (RaDaR) MPGN Cohort were included in this study
- RaDaR contains data on pediatric and adult MPGN patients from kidney units across the UK, with automated collection of retrospective and prospective laboratory and clinical data

Definitions and Clinical Measures

- Diagnosis was defined as the date of biopsy recorded in RaDaR
- eGFR calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula 2009[2] (adults) and the modified Schwartz formula[3] (pediatric)
- Kidney failure was defined as the first occurrence of either chronic kidney replacement therapy, or a sustained eGFR <15 mL/min/1.73 m^2

Eligibility Criteria

- Patients were included if they had a diagnosis date recorded in RaDaR.
- Patients were excluded from survival analyses if there was no follow up information following diagnosis, or patients had reached kidney failure prior to diagnosis.
- Patients were excluded from the eGFR slope analysis if they had less than 4 data points in the follow up period.

Statistical Analyses

- Rate of eGFR loss (eGFR slope) was calculated over the full duration of follow-up or until kidney failure or death. A linear mixed model was used to estimate each patient's intercept and slope of eGFR
- Kaplan-Meier estimates for kidney survival, from diagnosis to kidney failure, were calculated for each disease subgroup. The log-rank test was used for differences between group survival.
- Association of change in UPCR and kidney survival from diagnosis was evaluated using Cox regression

DISCUSSION

- We have described the clinical demographics and renal outcomes for 287 UK patients with IC-MPGN and C3G, and investigated associations with baseline proteinuria and change in proteinuria over 6-months to 1-year post diagnosis with renal outcomes.

Limitations

- The inclusion criteria for RaDaR-MPGN may lead to enrollment of patients with more progressive disease and thus may represent a higher risk population
- Reporting of proteinuria and eGFR data at disease onset is incomplete and may not be representative of the full cohort; however data are likely to be missing at random with limited bias

CONCLUSIONS

RaDaR is a large and robust data source allowing investigation into C3G/IC-MPGN natural history.

We found heterogeneity of current treatment approaches in this cohort and rapid progression to kidney failure despite current treatments.

Strong associations were found between UPCR change in the 6-to-12-month post diagnosis period and 20-year kidney survival.

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