International Journal of Research in Medical Sciences
Barai T et al. Int J Res Med Sci. 2025 Jul;13(7):2944-2953
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20252031

Original Research Article

Primary immune complex membranoproliferative glomerulonephritis and C3 glomerulonephritis: experience of two rare diseases from a single centre

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Received: 01 June 2025
Revised: 15 June 2025
Accepted: 16 June 2025

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ABSTRACT

Background: This study has been conducted to evaluate and compare the clinicopathological profile and treatment outcome of primary immune complex membranoproliferative glomerulonephritis (IC-MPGN) and C3 glomerulonephritis (C3 GN), two rare glomerular diseases and to find any predictive factors for renal and patient outcome.

Methods: A retrospective observational cross-sectional study, conducted at a tertiary care hospital. Patients with biopsy-proven MPGN were included after satisfying the inclusion and exclusion criteria. Detailed history, clinical examinations, laboratory investigations and kidney biopsy were noted. Outcome was recorded at months 3, 6, 12 and at the last available follow-up.

Results: Of the 24 subjects enrolled, 11 (45.8%) had primary IC-MPGN and 13 (54.2%) had C3 GN. Nephrotic syndrome is the prevalent presentation. No statistically significant difference was found in respect to clinical and biochemical parameters between two groups. Complement mediated group had more crescent and features of chronicity in renal biopsy. Renal and patient outcome was significantly better in immune mediated group compared to complement mediated group (log rank p=0.015); including complete remission (p=0.003), proteinuria reduction at 3 months (p=0.009), at the last known follow-up (p=0.005). During follow up, hematuria, higher serum creatinine and low median serum albumin were significantly more common in complement mediated group. No significant predictors were found for renal outcome and outcome was not influenced by treatment modality.

Conclusions: IC-MPGN and C3 GN are rare glomerular diseases. Although phenotypically similar, C3 GN showed poor outcome. Further multicentric study may help to better understand these diseases to find cost effective treatment.

Keywords: C3 GN, MPGN, Primary immune complex MPGN

INTRODUCTION

Membranoproliferative glomerulonephritis (MPGN) is a chronic, slowly progressive glomerular disease, characterized by distinct morphologic pattern. The name originates from histological alterations, including mesangial hypercellularity and the thickening of the glomerular basement membrane.[1] The incidence of MPGN varies in different parts of the world, but has shown a decline in most developed countries. The condition typically manifests in childhood but may occur at any age.[2] MPGN has recently been categorized into two distinct diseases: immune-complex MPGN (IC-MPGN) and C3 glomerulopathy (C3G), according to immunofluorescence results in kidney biopsies. C3 glomerulonephritis (C3 GN) is a subtype of C3G, characterized by predominant or exclusive C3 deposits, whereas combined immune-globulins and complement deposits in IC-MPGN.[3] IC-MPGN is classified as secondary when arising from an

underlying disease process. In absence of any identifiable cause, the lesion is considered "idiopathic" or "primary".[4] The incidence of idiopathic IC-MPGN is still unknown, although the estimated global annual incidence of C3G is between 1 and 3 cases per million people.[5] Patients with MPGN may present in one of four ways, as follows: nephrotic syndrome (40–70%); acute nephritic syndrome (20–30%); asymptomatic proteinuria and hematuria detected on routine urinalysis (20–30%); recurrent episodes of gross hematuria (10–20%).[6] Approximately 40% of children and young adults with renal function impairment may advance to end-stage renal disease within a decade.[7] Indicators of a negative prognosis encompass nephrotic syndrome, initial renal impairment, and sustained hypertension.[8]

No conclusive or targeted therapy of MPGN has been documented in the literature. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) may be utilized to manage proteinuria (conservative anti proteinuric therapy). Limited research has documented the application of glucocorticoids and other immunosuppressive drugs including calcineurin inhibitors, mycophenolate mofetil, azathioprine, and cyclophosphamide with variable results.

Despite advancement of clinical and basic research, little is known about MPGN in terms of clinical profile, pathological spectrum, diagnosis, optimal treatment and prognosis. Data is further limited from India focusing on MPGN. In this study, we aimed to find out the clinicopathological profile and treatment outcome of primary IC-MPGN and C3GN and we have attempted to find out differences between these two categories of MPGN. We also wanted to identify any predictive factors of renal outcome in terms of proteinuria response, decline in renal function and end-stage kidney disease (ESKD). This type of data is lacking in the literature, especially from India.

METHODS

This is a retrospective observational cross-sectional study, conducted in the Department of Nephrology of Institute of Post Graduate Medical Education and Research (IPGME&R) and SSKM Hospital Kolkata, one of the largest tertiary care centre of eastern India from October 2022 to September 2024.

Irrespective of age groups, patients with biopsy proven [light microscopy (LM) and immunofluorescence (IF)] MPGN pattern of renal injury attending the nephrology department were considered as study population. Patients with secondary MPGN such as patients with lupus nephritis (SLE), infectious diseases including hepatitis B virus, hepatitis C virus, shunt infection, other obvious infections, and light chain mediated disease and other underlying cause of disease were excluded. Also, patients not having their immune-fluorescence finding report, more than one biopsy (ambiguity of diagnosis) and patients untraceable for follow-up for more than 12 months were also excluded.

The objectives of the study were to determine the demographic and clinicopathological characteristics of primary IC-MPGN and C3 GN in our population and to identify the predictive factors of renal outcomes and prognosis. In this study, we tried to identify any differences in clinic-pathological profile and treatment outcome between these two types of membrano-proliferative glomerulonephritis.

Primary outcomes were decline in renal function as indicated by a 50% increase in serum creatinine from baseline and End stage kidney disease (ESKD) with renal replacement therapy (RRT) with patients on hemodialysis, peritoneal dialysis and renal transplant. Secondary outcome being complete proteinuria remission rate, defined as a 24-hour urinary protein of <0.3 g/day, or a urinary protein-to-creatinine ratio of <0.3 g/g Cr or in dipstick <1+ in 3 consecutive days at the last known follow-up date and the impact of therapy on decline in renal function or ESKD.

After approval of the Institutional Ethical Committee, study population were selected and recruited based on the inclusion and exclusion criteria after giving an informed written consent. All patients were required to have a diagnosis of C3 GN or IC-MPGN established through kidney biopsy. Old cases from biopsy registry and new cases during the study period were evaluated. Each patient was followed since their first hospital visit, for a minimum of 12 months (at 3 months, 6 months and 12 months, and the last available follow-up after diagnosis). The range of duration for follow-up was 12 months to 79 months.

Clinical data and biochemical parameters were noted at baseline and at each follow up. Clinical data included age (in years), gender, blood pressure (BP) and others. Blood investigations included total serum protein, serum albumin, serum creatinine, estimated GFR, serum C3 and C4 level. Complement factors estimated include complement C3, complement C4 and others. The machine model used for the purpose was Luminex® 200™. Urine examinations included urine routine and estimation of urine protein.

First clinical manifestations were classified as nephrotic syndrome, nephritic syndrome, rapidly progressive glomerulonephritis (RPGN), chronic GN.

Kidney biopsy reports were noted with LM and IF findings. Information regarding treatment including immunosuppression (steroid/steroid with MMF/ cyclo-phosphamide) or conservative therapy were also recorded. The Immunofluorescence was conducted by the microscope Magcam MU2A® by Magnus Opto Systems India Pvt. Ltd. During the data collection, standard definitions related to MPGN were used.

Statistical analysis

All data were entered in Microsoft excel sheet and statistical analysis was performed with statistical package for the social sciences (SPSS) version 20.0. Comparison between groups was performed by Chi-square test for categorical variables and the non-parametric Mann Whitney U test for continuous variables. To study prognostic factors, the end-point of this study were death or ESKD estimated by cox regression analysis where hazards odds ratio was analyzed with 95% confidence interval. Renal survival probabilities were determined using the Kaplan Meier method and group comparisons for median survival were performed using the log-rank test. Significance was set at $p<0.05$, except for univariate cox analysis where selection of factors was done for $p<0.2$.

RESULTS

In this study, we have evaluated 24 subjects with biopsy proven membranoproliferative (MPGN) pattern of injury, among which 11 (45.8%) were primary immune complex MPGN (IC-MPGN) and 13 (54.2%) were C3 GN. For primary IC-MPGN and C3 GN, median age of the patients were 28 years and 22 years (p=0.106) respectively and proportion of male participants were 72.7% and 46.2% respectively (Table 1). Nephrotic proteinuria, microhematuria, lower range of eGFR and higher serum creatinine were found quantitatively more in C3-MPGN. In renal biopsy sample, endocapillary proliferation was found more in primary IC-MPGN (100%), while C3GN had more crescentic pattern (53.8%) and more features of chronicity (IFTA) (Table 1). Conservative therapy and immunosuppressive drug use were significantly more in primary IC MPGN (p=0.033) and C3 GN group (p=0.033) respectively (Table 1).

At 3 months, 45.5% patients of primary IC MPGN achieved urinary protein <1 g/day compared to none with C3 GN and significantly more subjects with C3 GN had levels >3 g/day (p=0.014) (Table 2). Except for follow-up at 6 months, subjects of primary IC-MPGN group had a significantly better proteinuria reduction than C3 GN at 12 months, (p=0.027). Hematuria was significantly more in C3-MPGN (53.8%) than primary IC-MPGN (9.1%, p=0.033). Similarly, in C3 GN had significantly higher serum creatinine (p=0.015), lower median eGFR p=0.003) and lower median serum albumin (p=0.001). Proteinuria decreased drastically in primary IC-MPGN compared to C3 GN at 3 months (p=0.009) and at the last known follow-up [1.37 versus 0.15, (p=0.005)] (Table 2). Among the 9 patients who achieved C3>90 at 3 months, 7 (77.7%) were primary IC-MPGN. C3 normalization at 3 months is not significantly different (p=0.444) in 2 groups and immunosuppression did not make any significant impact in normalization of blood C3 level. Number of participants achieving complete remission was significantly more in primary IC-MPGN group (54.5%) compared to that of C3 GN (0%, p=0.003). Whereas C3 GN had more patients with partial remission, no remission, 50% rise of serum creatinine in the last visit, end stage kidney disease and death. 90.9% patient of primary IC MPGN had responded (CR or PR) in comparison to 38.5% of C3 GN cases (Table 2).

Regarding assessment of predictive factors for 50% rise of serum creatinine, age, 24-hour urine protein and serum albumin levels at baseline showed a significant hazard ratio of 0.886, 1 and 0.074 respectively ($p<0.2$) in univariate cox regression analysis. However, in multivariate analysis, these factors did not prove to be significant predictive factors for the rise in serum creatinine by 50% in the MPGN patients (Table 3). Evaluation of renal outcome by rise of creatinine of 50% between the two categories revealed no significant association between the type of MPGN and the survival probability of rise of creatinine (p=0.071) (Figure 2).

Table 4 showing cox regression analysis to find any predictive factor for progression to ESKD. None of the predictive factors taken for the cox regression univariate analysis were found to be significant ($p<0.2$) for making a multivariate model. Evaluation of renal outcome by progression to ESKD between the two study groups has found no significant association between the type of MPGN and the survival probability of progression to ESKD (p=0.138) (Figure 3).

Kaplan-Meier survival curves comparing renal outcome by proteinuria reduction to less than 1 g/day between two study groups showed that primary IC-MPGN patients had significantly higher probability of reduction of proteinuria to less than 1 g/day than C3 GN patients (p=0.015) (Figure 4).

Detailed evaluation of treatment effect on patient and renal survival was done in study population at large and in two groups separately. There was no significant association between the type of therapy received at baseline and the survival probability of rise of creatinine by 50% (p=0.292). Similarly, no significant association was detected between the type of therapy received at baseline and the survival probability of progression to ESKD (p=0.399). On the other hand, no significant association between the type of therapy received at baseline and the survival probability of reduction of proteinuria was found (p=0.457).

Effect of treatment modality was assessed separately in both the groups. Among the 11 patients with primary IC-MPGN followed up to a maximum period of 12 months, 9 patients achieved proteinuria reduction to less than 1 g/day, among whom 5 were receiving immunosuppression and rest 4 were receiving conservative therapy. There was no significant association between the type of therapy received at baseline and the survival probability of reduction of proteinuria (p=0.693). There was no rise of creatinine by 50%, or progression to ESKD, thus no survival analysis could be done.

13 patients with C3 GN followed up to a maximum period of 79 months showed 3 patients with rise in serum creatinine by 50% only in patients with baseline immunosuppressive therapy. However, there was no significant association between the type of therapy received at baseline and the survival probability of rise of creatinine (p=0.541). All the 3 patients with C3 GN showing progression to end stage kidney disease received immunosuppressive therapy at baseline. However, there was no significant association between the type of therapy received at baseline and the survival probability of progression to ESKD (p=0.642). Moving further, all the 4 patients with C3 GN who had proteinuria reduction to less than 1 g/day received baseline immunosuppressive therapy. But there was no significant association between the type of therapy received at baseline and the survival probability of reduction of proteinuria (p=0.371) among study participants with C3 GN.

Table 1: The clinicopathological spectrum and treatment profile in MPGN groups at baseline.

Categories	Primary IC MPGN (%)	C3 GN (%)	P value
Median (IQR) age in years	28 (35)	22 (18)	0.106*
Male	8 (72.7)	6 (46.2)	0.240**
Median (IQR) DBP in mmHg	90 (10)	80 (15)	0.186*
Median (IQR) duration between 1st symptom and consultation in days	21 (23)	30 (35)	0.207*
First clinical manifestation			
Nephrotic syndrome	5 (45.5)	6 (46.2)	0.996**
Nephritic syndrome	4 (36.4)	4 (30.8)	
Chronic GN	0 (0%)	0 (0%)	
RPGN	2 (18.1)	3 (23.0)	
24-hour urine protein (g/day)			
<1	1 (9.1)	0 (0)	0.518**
1–3	2 (18.2)	2 (15.4)	
>3	8 (72.7)	11 (84.6)	
Hematuria	8 (72.7)	10 (76.9)	1.000**
Pyuria	11 (100)	11 (84.6)	0.482**
Median (IQR) serum creatinine	1.5 (1.1)	1.6 (1.6)	0.608*
eGFR			
≥90	1 (9.1)	2 (15.4)	0.598**
60–89	4 (36.4)	3 (23.1)	
45–59	2 (18.2)	1 (7.7)	
30–44	3 (27.3)	3 (23.1)	
15–29	0 (0)	3 (23.1)	
<15	1 (9.1)	1 (7.7)	
Median (IQR) total protein	5.7 (1.1)	5.1 (1.0)	0.093*
Median (IQR) serum albumin	2.8 (0.9)	2.4 (1.1)	0.186*
Median (IQR) C3 level	85.9 (40)	68.2 (40)	0.063*
Median (IQR) C4 level	24.0 (20.1)	18.7 (19.7)	0.776*
Mesangial proliferation	11 (100)	13 (100)	-
Endocapillary proliferation	11 (100)	11 (84.6)	0.482**
Crescentic	4 (36.4)	7 (53.8)	0.392**
IFTA			
<25	10 (90.9)	10 (76.9)	0.556**
25–50	1 (9.1)	2 (15.4)	
>50	0 (0)	1 (7.7)	
Only conservative	5 (45.5)	1 (7.7)	0.033**
Immunosuppressive drugs (IS)			
Only steroid	6 (54.5)	3 (23.1)	0.206**
Steroid + MMF/cyclo	0 (0)	9 (69.2)	<0.001**
Total number of patients receiving immunosuppressive therapy	6 (54.5)	12 (92.3)	0.033**
Median (IQR) follow up duration in months	15 (9)	12 (21)	0.459*

IC-MPGN: Immune complex membranoproliferative glomerulonephritis, C3 GN-C3: glomerulonephritis, IQR: interquartile range, DBP: diastolic blood pressure, GN: glomerulonephritis, RPGN: rapidly progressive glomerulonephritis, IFTA: interstitial fibrosis tubular atrophy; *Clinically significant; **: Non-significant

Table 2: The renal outcome of subjects at follow-up periods.

Parameters	Primary IC MPGN	C3 GN	P value
3 months follow-up proteinuria			
24-hour urine protein (n=23) (g/day)			
<1	5 (45.5)	0 (0)	0.014**
1–3	4 (36.4)	4 (33.3)	
>3	2 (18.2)	8 (66.7)	
6 months follow-up proteinuria			
24-hour urine protein (n=19) g/day			
<1	7 (70.0)	4 (44.4)	0.413**
1–3	1 (10.0)	3 (33.3)	
>3	2 (20.0)	2 (22.2)	
12 months follow-up proteinuria			
24-hour urine protein (n=17) (g/day)			
<1	8 (88.9)	2 (25)	0.027**
1–3	1 (11.1)	5 (62.5)	
>3	0 (0)	1 (12.5)	
Last known follow-up proteinuria			
24-hour urine protein (n=24) (g/day)			
<1	8 (72.7)	1 (7.7)	0.005**
1–3	2 (18.2)	8 (61.5)	
>3	1 (9.1)	4 (30.8)	
At last known visit			
Hematuria	1 (9.1)	7 (53.8)	0.033**
Median (IQR) serum creatinine	1 (0.62)	2.7 (2.65)	0.015*
Median (IQR) eGFR	85.3 (57.4)	24.1 (49.3)	0.003*
Median (IQR) serum albumin	4.2 (0.6)	2.9 (0.65)	0.001*
Proteinuria remission			
Baseline	5.20	4.15	0.392
At 3 months follow-up	0.80	2.85	0.009
At 6 months follow-up	0.15	1.09	0.079
At 12 months follow-up	0.15	1.40	0.008
At last follow-up	0.15	1.37	0.005
Disease outcome			
Complete remission	6 (54.5)	0 (0)	0.003
Partial remission	4 (36.4)	5 (38.5)	1.000
No remission	0 (0)	3 (23.1)	0.223
50% rise of creatinine in the last visit	0 (0)	3 (23.1)	0.223
ESKD	0 (0)	3 (23.1)	0.223
Death	1 (9.1)	3 (23.1)	0.596

IC-MPGN: Immune complex membranoproliferative glomerulonephritis, C3 GN: C3 glomerulonephritis, IQR: interquartile range, ESKD: end stage kidney disease; *Clinically significant; **: Non-significant

Table 3: Cox regression analysis of renal outcome for predicting the rise of serum creatinine by 50% in all patients (n=24).

Variables	Univariate			Multivariable		
	HR	CI	P value	HR	CI	P value
Age (per year)	0.886	0.742–1.059	0.185	0.956	0.795–1.149	0.631
Gender (male)	1.035	0.093–11.490	0.978	-	-	-
SBP (per mmHg)	0.967	0.909–1.029	0.288	-	-	-
24 hour-urine protein at baseline (per g/dl)	1.000	1.000–1.000	0.153	1.000	1.000–1.001	0.244
Serum albumin at baseline (per g/dl)	0.074	0.006–0.968	0.047	0.032	0.000–7.393	0.216

Continued.

Variables	Univariate			Multivariable		
	HR	CI	P value	HR	CI	P value
eGFR	0.998	0.966–1.031	0.923	-	-	-
Therapy (immunosuppression)	32.402	0.001–1787541.99	0.532	-	-	-

HR: Hazard ratio, CI: confidence interval, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate

Table 4: Cox regression analysis of renal outcome comparison of progression to ESKD (n=24).

Variables	Univariate		
	HR	CI	P value
Age (per year)	1.025	0.967–1.087	0.410
Gender (male)	42.807	0.002–750586.824	0.451
SBP (per mmHg)	1.034	0.971–1.101	0.301
24 hour-urine protein 1st visit (per g/dl)	1.000	1.000–1.000	0.880
Serum albumin 1st visit (per g/dl)	0.314	0.047–2.094	0.232
eGFR	0.984	0.940–1.031	0.499
Therapy (immunosuppression)	32.374	0.000–20928411.2	0.610

HR: Hazard ratio, CI: confidence interval, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate

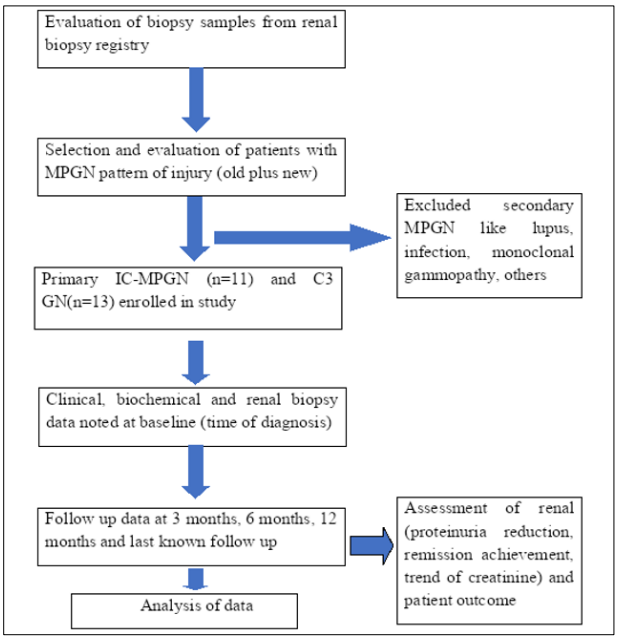

Figure 1: Flow chart of study design.

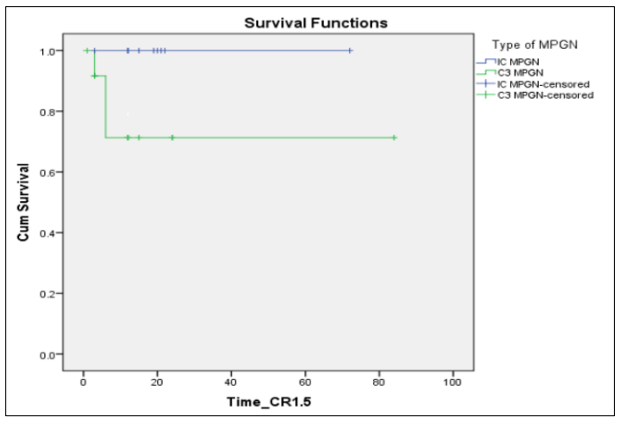

Figure 2: Comparison of renal outcome by rise of creatinine of 50% between IC-MPGN and C3 GN.

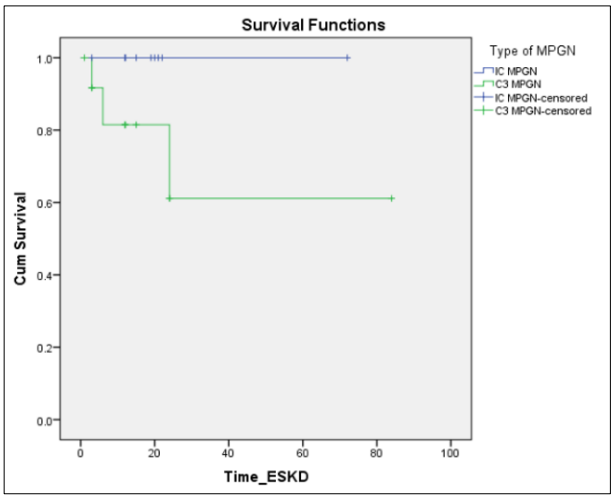

Figure 3: Comparison of renal outcome by progression to ESKD.

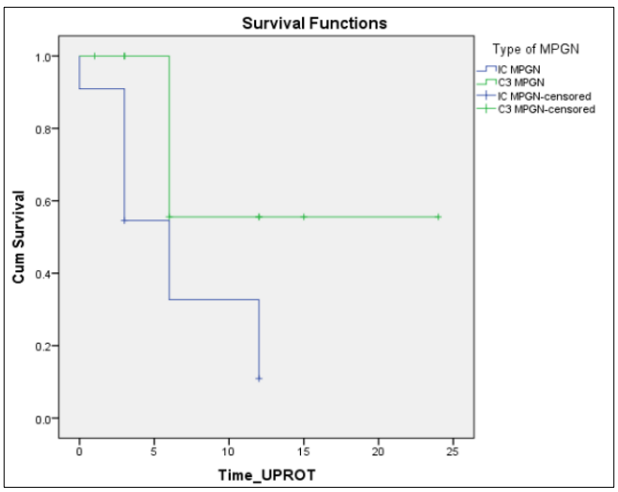

Figure 4: Kaplan-Meier survival curves comparing renal outcome by proteinuria reduction to less than 1 g/day between IC-MPGN and C3 GN.

DISCUSSION

Objectives of the current study were to explore and compare the demographic, clinical and laboratory characteristics of primary immune complex membrano-proliferative glomerulonephritis (IC-MPGN) and C3 GN in our population and to identify the predictive factors of renal outcome and prognosis of these two subtypes of MPGN.

Out of 24 patients enrolled in the study, 11 (45.8%) had primary IC-MPGN and rest 13 (54.2%) had C3-MPGN and the median age of the participants being 28 and 22 years respectively (p=0.106). Gender wise, 72.7% of primary IC-MPGN were males compared to 46.2% of C3-MPGN (p=0.240). Most of the studies on MPGN have been carried out on children.[9,10] Majority of the studies had age range 13 months–15 years, such as in study by Cansick et al, who followed them for a median period of 3.5 years.[8] Majority of studies in adult MPGN are retrospective in nature. Briganti et al did a retrospective review of the histopathology reports of renal biopsies performed in Victoria, Australia from 1995 to 1997 in adults and found that the diagnosis of MPGN was significantly more common in males than females (OR: 2.23; 95% CI: 1.51, 3.29) and incidence was greater between 55 and 74 years.[11] Bombac et al carried out a study on a large United States cohort of 111 patients having C3 glomerulopathy. Both C3GN and DDD were diagnosed majorly within the age group of 18 to 50 years, while the male-female ratio is similar in both (63.2/36.8 versus 66.7/33.3, p=0.8).[12]

Although no significant difference in clinical and laboratory parameters were found, primary IC-MPGN had higher median blood pressure (140/90 mmHg) compared to C3 GN (130/80 mmHg). Nephrotic syndrome was the most common presentation in both the groups, followed by Nephritic syndrome. C3 GN shoed higher level of proteinuria, hematuria, lower eGFR, high average serum creatinine (median 1.6), lower serum albumin and lower C3 level compared to primary IC-MPGN. Analysis of renal histopathology revealed similar prevalence of mesangial proliferation in both the groups but the endocapillary proliferation was found more in primary IC-MPGN (100%), while crescent and high IFTA was found more in C3 GN. In a study by Nakano et al, proteinuria was found to be much higher in the primary IC-MPGN group (p=0.0063), which is in contrast to our study result. Studies have shown significantly lower serum C3 value in the complement mediated MPGN group (p=0.0317), similar to our findings.[13] Kawasaki et al found that among 19 patients diagnosed with IC-MPGN (group 1) and 18 patients diagnosed with C3GN (group 2), the urinary protein excretion, incidence of hematuria, low serum C3 values, and scores for mesangial proliferation and interstitial fibrosis were higher in group 2 than in group 1.[14]

In our study, number of participants treated with immunosuppressive drugs were significantly more in C3 GN group. At follow up, proteinuria reduction was significantly better in primary IC-MPGN group at 3 months (p=0.009) and at the last known follow-up (p=0.005). Except for follow-up at 6 months, the primary IC-MPGN group had a significantly better proteinuria reduction to <1 g/day than C3 GN at 12 months (p=0.027) and at the last known follow up. Further follow up data showed C3 GN had significantly more hematuria (53.8% versus 9.1%; p=0.033), higher median serum creatinine (p=0.015), lower median eGFR (p=0.003) and significantly lower median serum albumin (p=0.001) than primary IC-MPGN. Only 9 patients had their C3 levels increased to >90 at 3 months, of whom 7 (77.7%) were IC-MPGN. Regarding final renal outcome, percentage of subjects achieving complete remission was significantly higher in IC-MPGN group (54.5%) compared to that of C3-MPGN (0%) (p=0.003),

Okuda et al compared both types of MPGN in 14 children. Four children diagnosed with classical or immune-complex mediated MPGN and 7 with C3GN underwent methylprednisolone pulse therapy, succeeded by a two-year regimen of oral prednisolone. Consequently, six out of seven children with C3GN underwent combined therapy (prednisolone, azathioprine, and anticoagulants) for two years due to inadequate response to oral prednisolone. During their latest follow-up, two children diagnosed with IC-MPGN and seven with C3GN had not attained remission.[15] Woo et al however found no significant difference in the incidence of progressive renal dysfunction between the two types (p=0.447).[16] Iatropoulos et al indicated that nephrotic syndrome and significant histological damage might have elevated the risk of progression to ESKD in a substantial Italian cohort of 140 adult and pediatric patients with idiopathic IC-MPGN and C3G.[17]

Nakagawa et al found that about 80% of the patients in both their groups were treated with immunosuppressive therapy till last follow-up period.[18] Conversely to our study findings, here after a median follow-up of 4.8 years, the complete remission rate of proteinuria was significantly higher in patients with C3GN (64.3%) than in those with IC-MPGN (29.9%; p=0.015).

Kirpalani et al observed a trend of elevated serum creatinine levels in patients with C3G compared to those with IC-MPGN, both at diagnosis and after a mean follow-up of 4 years, although the estimated glomerular filtration rate (eGFR) did not differ significantly.[9] Steroid treatment resulted in a notable enhancement in eGFR compared to no steroids in C3G, but did not show improvement in IC-MPGN. Kidney function was maintained in both groups; however, hypertension persisted in 42.5% of the cohort at the final follow-up, and the urine protein/creatinine ratio remained increased [mean 253.8 (range 91.9–415.7) mg/mmol].[10]

In the present study, he renal outcome significantly improved in 9 patients (81.8%) of primary IC-MPGN with

proteinuria decreasing to <1 g/day, and the median survival rate being 6 months (95% confidence interval 2.9–9.0 months) compared to 4 patients (30.76%) in C3 GN (log rank p=0.015). Three patients only in C3 GN (23.1%) had a rise in serum creatinine by 50% and also progressed to ESKD, with no significant log-rank difference found with IC-MPGN. There was no overall significant difference between the median survival rate for immunosuppressive therapy in reducing proteinuria i.e., 6 months (95% CI 3.9–8.1 months) and for conservative therapy for the same, i.e., 6 months (95% CI 0.12–11.8 months). Even only under IC-MPGN, the median survival time for conservative therapy was 6 months (95% CI 1.3–10.7 months) compared to 3 months for immune-suppressive therapy, but did not significantly differ. Whereas under C3 GN, all the 4 proteinuria reduction events under immunosuppressive therapy happened at 6 months compared to none with conservative therapy. Thus, mode of treatment did not seem to make much of a difference in renal survival rate in our study cohort. In univariate cox regression analysis for predicting renal outcome via rise of serum creatinine by 50%, we found that age [HR=0.886, 95% CI: 0.742–1.059], 24-hour urine protein at baseline [HR=1] and serum albumin levels [HR=0.074, 95% CI: 0.006–0.968] showed significant hazard ratios (p<0.2) but failed to be significant predictors in the multivariable model.

Bomback et al previously identified a 40% progression rate to advanced CKD, ESKD, or mortality in a substantial American cohort study comprising 111 individuals with C3G, about one-third of whom were pediatric cases. In multivariable models, the most significant indicators for progression were the eGFR at diagnosis and the presence of tubular atrophy/interstitial fibrosis (IFTA).[12] Our univariate or multivariable model however did not find any significant predictors for progression to ESKD.

In the final follow-up assessment conducted by Kawasaki et al involving 37 pediatric patients, the proportion of individuals classified as non-responders or with end-stage renal disease was greater among those with C3 glomerulonephritis compared to those with IC-MPGN.[14]

In a retrospective study by Aksoy et al in Turkey, 20 with IC-MPGN and 15 with C3G were monitored for a length of 68 months. Complete remission was observed in 14 patients (40%) [7 (35%) with IC-MPGN and 7 (46.6%) with C3G], but only 5 patients (25%) in the MPGN group achieved partial remission (p=0.112). The Kaplan-Meier analysis indicated kidney survival rates of 85% for the IC-MPGN group and 80% for the C3G group, with a p value of 0.800. In multivariate cox regression analysis, haemoglobin [p=0.046, HR: 0.750 (0.566-0.995)] and baseline eGFR levels [p=0.011, HR: 0.981 (0.967-0.996)] were identified as predictors of complete or partial remission.[19]

In a mixed adult-pediatric cohort study of patients with C3G, Meena et al demonstrated a significant prolongation in the time to ESKD in patients administered steroids compared to those who did not receive steroid therapy at diagnosis, with the protective effect of steroid therapy remaining significant in the multivariate analysis.[20]

Woo et al took eGFR as a measure of progressive renal function deterioration and showed that among the patients on immunosuppressants, 5 had a total of 50% decrease in eGFR. During the follow-up period, six patients succumbed to cancer (four patients) or hepatorenal disease.[16]

In the investigation carried out by Kirpalani et al in involving solely pediatric patients, severe CKD and ESKD were infrequent occurrences, observed in merely 7.3% of C3G patients, 5.7% of IC-MPGN patients, and 12.5% of the whole cohort achieving an estimated glomerular filtration rate (eGFR) of ≤15 ml/min per 1.73 m² at the final follow-up (average duration of 4 years), with no recorded fatalities. No difference in eGFR was seen between patients administered steroids and those who did not receive first steroid therapy.[10]

Nakagawa et al had found that the renal survival rate significantly differed between patients with IC-MPGN and C3GN (73.1% versus 100%; log-rank p=0.031). No individuals with C3GN experienced a 50% increase in serum creatinine, advanced to end-stage kidney disease, or succumbed. The rate of rise in serum creatinine was markedly greater in individuals with IC-MPGN compared to those with C3GN (43.9% versus 0.0%, log-rank p=0.006).[18]

Even though most other studies were carried out only on C3GN and pediatric patients, our study yielded similar results with almost all other published literature. Results of our study showed some differences when comparing with existing literature regarding clinical profile, treatment response, patient and renal survival. This might be due to complex nature of the disease under evaluation, relatively rare nature of disease, variable sample size of study participants, heterogenicity regarding ethnicity, lack of consensus definitive treatment.

Limitations

In spite of every sincere effort, the present study has some lacunae. Single centre study, smaller study population and the retrospectively collected data for most of the participants are major limitations. The predictors for renal outcomes could not be elicited probably due to lesser sample size. Other tests such as electron microscopy could have provided a better picture of the renal pathology and outcome.

CONCLUSION

From this study we conclude that, compared to primary IC MPGN, C3 GN occurred in patients with lower age with female preponderance. C3 GN showed higher incidence of

proteinuria, hematuria, reduced eGFR and increased serum creatinine at baseline, although there has been no significant difference with primary IC-MPGN. Compared to primary IC MPGN, C3 GN group had more crescents and more interstitial fibrosis and tubular atrophy. Although there was no major difference in clinical presentation between IC-MPGN and C3 GN, significant renal survival and patient outcome improvement noticed in primary IC-MPGN compared to C3 GN patients. However, no significant predictive factors were found for renal outcome in the two subtypes of MPGN and mode of therapy had no effects on renal outcome on the study population at large and separately in both the groups. Overall, our study showed worse renal and survival outcomes for C3 GN than primary IC MPGN patients. Result of the present study may invite further research with large population with more insight in disease pathophysiology, better understanding of the epidemiology, natural course and intervention outcome from Indian subcontinent.

ACKNOWLEDGEMENTS

Authors would like to thank all the support staffs of Department of Nephrology IPGME&R, SSKM Hospital and all the participants who participated in the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Barai T, Bhatttacharjee K, Basu K, Dasgupta S. Primary immune complex membranoproliferative glomerulonephritis and C3 glomerulonephritis: experience of two rare diseases from a single centre. Int J Res Med Sci 2025;13:2944-53.