

Natural History and Clinical Associations with Long-Term Outcomes in Primary C3 Glomerulopathy and Immune Complex-Mediated Membranoproliferative GN

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Key Points

- This retrospective study analyzed clinical, histological, and biochemical data from a large cohort of participants with biopsy-proven primary C3 glomerulopathy/immune complex-mediated membranoproliferative GN.
- C3 glomerulopathy and immune complex-mediated membranoproliferative GN subjects shared most baseline and longitudinal features; 10-year kidney survival did not differ across histological subtypes.
- Older age at onset and higher proteinuria levels at 1 year from biopsy were the strongest predictors of kidney failure.

Abstract

Background Membranoproliferative glomerulonephritides (MPGNs) are defined by a typical glomerular histopathological pattern including C3 glomerulopathy (C3G) and immune complex-mediated MPGN (IC-MPGN). The overall prognosis is poor and the treatment options remain limited. Outcome predictors and reliable surrogate endpoints are critically needed for interventional trials. Herein, we described the natural history and analyzed clinical, histological and biochemical data from a large cohort of patients with primary C3G/IC-MPGN.

Methods This is a retrospective analysis of patients with biopsy-proven primary C3G or IC-MPGN from the Italian Registry of MPGN. Demographic, clinical and histopathological data, molecular complement profiles, treatment patterns, and outcomes were collected. We performed univariable and multivariable Cox regressions and Kaplan–Meier survival analyses to assess risk associations with kidney disease progression. The composite endpoint included ESKD (defined by either eGFR <15 ml/min per 1.73 m², initiation of chronic dialysis or kidney transplantation), doubling of serum creatinine at the last available follow-up, or death by kidney-related causes.

Results Of the 349 patients identified, 208 had C3G and 141 IC-MPGN. Females were 41%, and over half were younger than 18 years old at time of biopsy. C3G and IC-MPGN patients shared most baseline and longitudinal features, with IC-MPGN patients presenting with higher baseline proteinuria (median 4.0 versus 2.3 g/24 hours, $P < 0.001$). Median eGFR at presentation was 83 ml/min per 1.73 m². Twenty-six percent of patients progressed to ESKD over a median follow-up of 5 years from diagnosis. Higher proteinuria levels at 1 year from biopsy, particularly ≥ 1 g/24 hours, were significantly associated with a higher risk of adverse kidney outcomes. Pediatric onset was associated with better kidney survival, whereas kidney survival at 10 years did not statistically differ across histological subtypes. Complement dysregulation and rare functional variants in complement genes were not associated with outcomes.

Conclusions Our findings from a large and well-characterized cohort of individuals with primary C3G/IC-MPGN identify age at onset and proteinuria levels as associations with kidney survival, a finding that should inform future interventional trials.

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Introduction

Membranoproliferative glomerulonephritides (MPGNs) are a heterogeneous group of nephropathies defined by a typical glomerular histopathological pattern of mesangial hypercellularity, endocapillary proliferation, and duplication of the glomerular basement membrane.¹

Primary MPGN forms are rare and predominantly affect children and young adults.² Key drivers of the glomerular injury are genetic or acquired dysregulations of the complement pathway leading to the deposition of complement fragments in the glomeruli with consequent inflammatory response.^{3–5} Secondary causes like infections, autoimmune diseases, or monoclonal gammopathies can lead to the same histological pattern and must be included in the diagnostic workup because they may be amenable to specific treatments.⁶

In an attempt to reflect the underlying pathophysiology, MPGNs have been reclassified over time. The current immunofluorescence (IF)-based classification differentiates between immune complex-mediated MPGN (IC-MPGN), characterized by glomerular deposition of both immunoglobulins and complement components, and C3 glomerulopathy (C3G), characterized by dominant C3 deposits. C3G is further classified into C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) on the basis of deposits appearance at the electron microscopy (EM).^{6–8} Notably, a shift in histological subtypes demonstrated in patients with longitudinal biopsies suggest a possible evolution from one form to the other and points to the limits of a histology-based classification in capturing the underlying pathophysiology.

While clinical presentation and outcomes of primary MPGNs are variable, ranging from asymptomatic urine abnormalities to acute or rapidly progressive GN, the overall prognosis is poor, with progression to ESKD seen in about 40% of cases.^{9–11} Despite advances in understanding this condition, treatment options remain limited.^{12,13} Recently, building on the success of the anti-C5 antibody eculizumab for treating complement-mediated diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, research exploring various terminal and upstream complement inhibitors in primary C3G/IC-MPGN has developed, aiming to target the underlying pathological process.¹⁴ Eculizumab has not proven to be as efficacious as initially showed.¹⁵ A recently published trial comparing avacopan, a C5a receptor inhibitor, versus placebo did not meet its primary endpoint.¹⁶ The anti-factor B iptacopan recently received US Food and Drug Administration and European Medicines Agency approval as the first treatment for adults with C3G after results from the phase 3 APPEAR-C3G trial showing significant proteinuria reduction at 6 months and an acceptable safety profile.^{17,18} The trial is still ongoing in adolescents. Shortly thereafter, the anti-C3 agent pegcetacoplan was approved by the US Food and Drug Administration for adolescents and adults with C3G and IC-MPGN, including post-transplant recurrence. This approval was based on the results of the phase 3 VALIANT trial, which demonstrated a significant reduction in proteinuria at 6 months and a favorable safety profile.^{19,20}

The extremely heterogeneous progression of MPGNs might affect the sensitivity of ESKD as an endpoint to

reliably describe disease outcome and its response to new therapies. In line with a meta-analysis supporting the use of proteinuria reduction as a surrogate endpoint in IgA nephropathy,²¹ a retrospective study by the Spanish Group for the Study of Glomerular Diseases on 149 cases with primary C3G and IC-MPGN demonstrated an association between proteinuria lowering and improved kidney outcomes.²² A recent paper on a large C3G/IC-MPGN cohort from the United Kingdom Registry of Rare Kidney Diseases (RaDaR) showed that a halving of urinary protein-to-creatinine ratio (UPCR) at 12 months from baseline was associated with lower risk of kidney failure, and patients with a UPCR <100 mg/mmol had a substantially lower risk.^{23,24} Similar results were reported in a recent multinational work, whereas studies on smaller cohorts showed inconsistent results.^{25,26}

The need to identify appropriate trial outcomes for complement-mediated glomerulopathies has been the focus of several scientific workshops in recent years.^{27–29} However, definitive predictors of long-term kidney outcomes, as well as early and intermediate surrogate endpoints as efficacy measures for interventional trials in primary MPGNs require further validation.

To address this clinical need, we analyzed clinical, histological, and biochemical data from a large cohort of primary C3G/IC-MPGN patients retrieved from the Italian Registry of MPGN to evaluate whether and to what extent these parameters and their changes can predict long-term kidney outcomes.

Methods

Study Population and Histopathological Characterization

Patients with a histological diagnosis of C3G/IC-MPGN were selected from the Italian Registry of MPGN, which is coordinated by the Clinical Research Center for Rare Diseases Aldo e Cele Daccò at the Istituto di Ricerche Farmacologiche Mario Negri Istituto di Ricovero e Cura a Carattere Scientifico in Bergamo, Italy (<https://www.marionegri.it/eng/mpgn-c3g-registry>). Since 2006, this registry has collected data and biological samples from MPGN patients referred by several Italian nephrology units. Samples were stored in the Biobank for Rare Diseases and Kidney Diseases at the Mario Negri Institute Biological Resources Center (Ranica, Bergamo). The study was approved by the local Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Patients signed an Institutional Review Board-approved informed consent form.

Patient selection and histological scoring are detailed in the [Supplemental Methods](#). Briefly, patients with secondary causes of C3G/IC-MPGN—autoimmune diseases, monoclonal gammopathies, hepatitis B virus, hepatitis C virus, and HIVs infections or typical postinfectious GN—or an old, inconclusive biopsy or without IF were excluded. Kidney biopsy reports were centrally reviewed and scored by an independent nephropathologist. Patients with primary MPGN were diagnosed as either IC-MPGN or C3G according to the current classification.⁷ C3G cases were further classified as C3GN or DDD by EM ([Figure 1](#)).

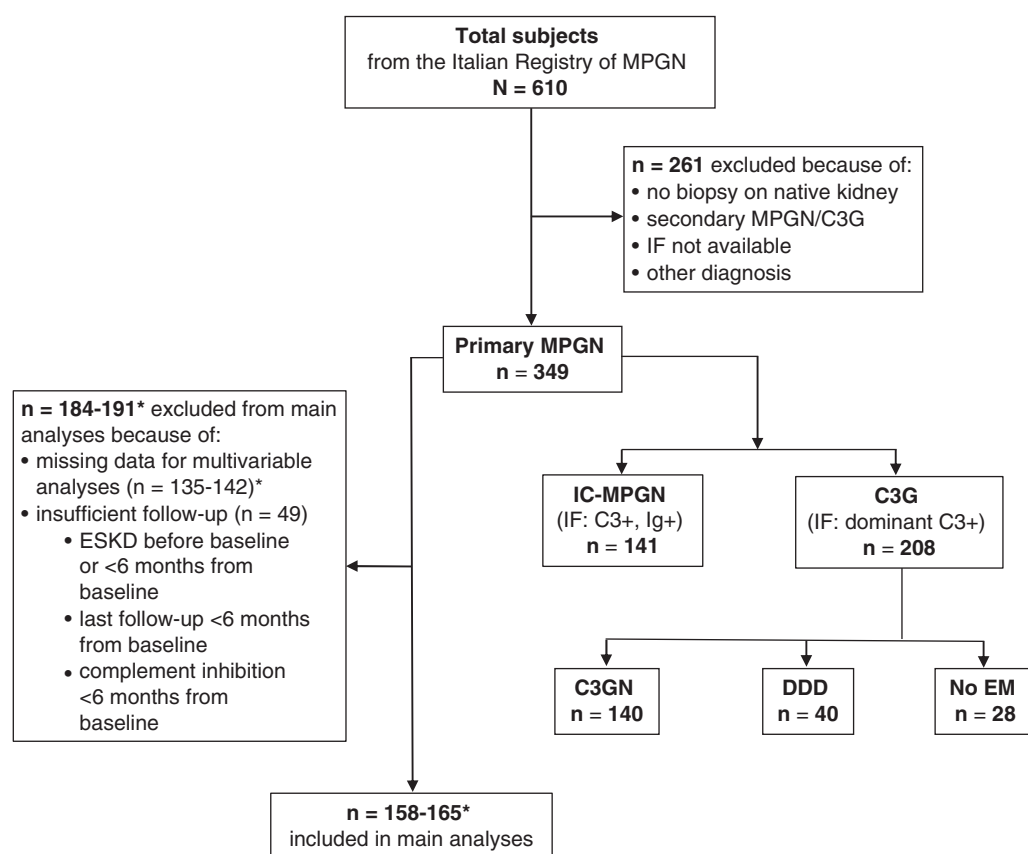


Figure 1. Flowchart of patient selection from the Italian Registry of MPGN. Out of a total of 610 patients in the registry, 349 were identified with biopsy-proven primary MPGN. Patients with secondary causes of MPGN, an older, inconclusive biopsy or without IF were excluded. According to the current classification, patients with primary MPGN were diagnosed as either IC-MPGN or C3G on the basis of IF (C3 staining intensity in C3G ≥ 2 of magnitude than any other immune reactants). Within the C3G group, further classification into C3GN or DDD was determined by EM (although this was unavailable for 28 patients with C3G). *Of the 349 patients, 49 were excluded from the analyses because of insufficient follow-up (ESKD before baseline or within 6 months thereafter, last follow-up <6 months from baseline, or treated with complement inhibitors within 6 months from baseline). Patients with missing data for any variables required by each specific multivariable model were excluded from that analysis, resulting in a different number of patients included in each model: In the multivariable model assessing the association between progression to the composite endpoint and 1-year proteinuria, 165 patients were included; in the model assessing the association with proteinuria change from baseline to 1-year follow-up, 158 patients were included; in the model assessing the association with the 1-year eGFR, 162 patients were included. C3G, C3 glomerulopathy; DDD, dense deposit disease; EM, electron microscopy; IC-MPGN, immune complex-mediated membranoproliferative GN; IF, immunofluorescence; MPGN, membranoproliferative GN.

Clinical and Biochemical Parameters

Demographic, clinical, and biological parameters were collected at disease onset, baseline (time of first diagnostic biopsy), 1 year from baseline (values recorded between 6 and 18 months from baseline), and last available follow-up. In patients treated with complement inhibitors, the last available pretreatment laboratory values and outcomes were used as the last follow-up parameters, to avoid the confounding effect of these disease-modifying medications on the disease course. ESKD and deaths were recorded. Most patients underwent extensive complement profiling at the Istituto di Ricerche Farmacologiche Mario Negri Istituto di Ricovero e Cura a Carattere Scientifico. Further details are provided in [Supplemental Methods](#).

Statistical Analyses

Descriptive statistics are presented as median (interquartile range), mean (SD), or frequency (count), as appropriate.

Comparisons of population characteristics by histopathological categories and by age at onset were performed using the Student *t* test, Mann-Whitney *U* test, or Fisher exact test according to the variable type and distribution. Statistical significance was defined as a *P* value < 0.05.

The composite endpoint for the main analyses included ESKD (defined by either eGFR <15 ml/min per 1.73 m², initiation of chronic dialysis or kidney transplantation), doubling of serum creatinine level at last available follow-up versus baseline or death by kidney causes. In patients younger than 18 years at baseline, the composite endpoint excluded the doubling of creatinine to avoid misattributing growth-related increases to a poor kidney outcome. The main analyses were performed using multivariable Cox regressions to evaluate the associations between progression to the composite endpoint and (1) proteinuria at 1 year from baseline, (2) proteinuria change from baseline to 1-year follow-up, (3) 1-year eGFR. The

covariates included IF-based histological diagnosis, demographic parameters (age at onset, biological sex), C3 nephritic factors (C3NeFs) positivity, the presence of rare functional variants in complement genes, a positive family history of complement-mediated disease, clinical features at onset (arterial hypertension, edema), interval from onset to baseline, histological and treatment data. Patients with insufficient follow-up (ESKD before baseline or within 6 months thereafter, follow-up <6 months from baseline, or treated with complement inhibitors within 6 months from baseline) or missing data were excluded. No imputation or other statistical computation was performed.

The correlation between proteinuria at 1 year and eGFR at the last follow-up was also evaluated. The association between different ranges of 1-year proteinuria and kidney outcomes was then evaluated by running three separate univariable Cox regressions, each time dividing the patients into two groups based on different thresholds: 0.3 g/24 hours (remission threshold); 1 g/24 hours (reference target in current interventional trials in C3G/IC-MPGN); and 3.5 g/24 hours (nephrotic-range proteinuria).

Kaplan–Meier survival analyses were conducted by censoring kidney survival data at 10 years, using different explanatory variables: 1-year proteinuria (considering a cut-off of 1 g/24 hours), age of onset (cut-off at 12 and 18 years), IF-based histological category, the presence of rare functional variants in complement genes, and/or positive family history for complement-mediated diseases. Patients with ESKD before baseline were not considered in survival analyses.

Results

Study Population

Of the 610 total cases in the registry, 349 patients with biopsy-proven primary MPGNs were identified, of which 141 (40%) had a diagnosis of IC-MPGN and 208 (60%) of C3G. Of these 208 patients, 140 (67%) had C3GN and 40 (19%) DDD. EM was unavailable in the remaining 28 C3G cases (Figure 1).

Female patients represented 41% of the population and were equally distributed across histological subgroups. Median age at disease onset was 15 years, ranging from 1 to 72 years. Diagnosis occurred at a median age of 16.6 years, with a median time from onset to baseline of almost 6 months. Children younger than 12 years at baseline represented almost a third of the population (Table 1).

Clinical presentation at onset was characterized by hematuria in most cases (85%) across all diagnostic subgroups. Nephrotic-range proteinuria at onset was significantly more frequent in IC-MPGN than in patients with C3G (58% versus 37%, $P < 0.001$), as confirmed by significantly higher median proteinuria (4.0 versus 2.3 g/24 hours, $P < 0.001$) and lower median serum albumin (2.9 versus 3.5 g/dl, $P < 0.001$) in IC-MPGN than in patients with C3G at baseline. Over 40% of cases were hypertensive at onset, with no significant differences across histological groups. Kidney function at onset ranged from normal to acute kidney failure, with a median eGFR of 83 ml/min per 1.73 m² (Table 1).

Supplemental Table 1 presents a detailed cohort description by age at onset. No significant differences were observed in sex distribution, histological classification, or time from onset to baseline across age subgroups. Hematuria was significantly more frequent in patients with onset before 18 years (92% versus 73%, $P < 0.001$). Nephrotic-range proteinuria (56% versus 37%, $P = 0.004$), lower kidney function (eGFR=74 versus 90 ml/min per 1.73 m², $P < 0.001$), and arterial hypertension (53% versus 35%, $P = 0.002$) at onset were significantly more prevalent in patients with adult onset.

Thirteen of 349 patients progressed to ESKD within 14 months from onset (Supplemental Table 2).

Complement Studies

Low serum C3 and C4 levels were observed in 84% and 30% of cases, respectively, with a similar frequency across histological subgroups for low C3, whereas a borderline significantly higher frequency of low C4 was found in IC-MPGN than C3G (36% versus 25%, $P = 0.05$). Median soluble terminal complement complex (sC5b-9) was elevated and significantly higher in C3GN than in patients with DDD (490 versus 286 ng/ml, $P = 0.04$). C3NeFs positivity was significantly more prevalent in patients with DDD than C3GN (75% versus 28%, $P < 0.001$). The prevalence (15%) of rare functional variants in complement genes was similar across histological categories, and rare variants in complement factor H and C3 were the most frequent ones. Variants in complement factor B were only identified in four IC-MPGN cases (Table 1). A higher percentage of patients with onset before 18 years had low serum C3 (90% versus 75%, $P < 0.001$), low C4 (36% versus 20%, $P = 0.002$), and C3NeF positivity (46% versus 28%, $P = 0.002$) at initial measurement. Pediatric patients also showed higher median sC5b-9 levels (598 versus 303 ng/ml, $P \leq 0.001$; Supplemental Table 1).

Histological Parameters

At the first diagnostic kidney biopsy, signs of disease activity, with a median score of mesangial proliferation of 2 on a scale of 3, mild endocapillary proliferation and interstitial inflammation, were relatively frequent across all cohort. Crescents were rare. Chronicity markers were mild, with around 10% of sclerotic glomeruli, very mild arteriolar sclerosis, and interstitial fibrosis. Notably, chronic lesions were statistically more frequent in patients with adult onset (Table 1 and Supplemental Table 1).

Follow-Up

After the biopsy, patients were followed for a median of 60 months (range: 0–529), with a significant longer median follow-up in patients with pediatric onset ($P = 0.03$). Median proteinuria at 1 year remained significantly higher in patients with IC-MPGN than in those with C3G (1.3 versus 0.7 g/24 hours, $P = 0.004$). Median changes of proteinuria between baseline and 1 year did not statistically differ between IC-MPGN and C3G, regardless the onset age (Table 1 and Supplemental Table 1).

Almost 26% of patients progressed to ESKD, without statistical difference across histological categories. There were 11 deaths, of which only one attributed to clear kidney-related causes.

Table 1. Full cohort description

Cohort Characteristics	Patients with Available Data, <i>n</i> (%)	Primary MPGN, all (<i>n</i> =349)	IC-MPGN (<i>n</i> =141)	C3G ^a (<i>n</i> =208)	DDD (<i>n</i> =40)	C3GN (<i>n</i> =140)
Females, <i>n</i> (%)	349 (100)	143 (41)	61 (43)	82 (39)	15 (38)	57 (41)
Age at onset, yr	346 (99)	15 (10–25)	16 (10–33)	14 (10–22)	13 (10–22)	15 (9–22)
Children younger than 12 yr, <i>n</i> (%)		108 (31)	41 (29)	67 (32)	16 (40)	45 (32)
Adolescents 12–17 yr, <i>n</i> (%)		85 (24)	30 (21)	55 (26)	10 (25)	34 (24)
Age at baseline (biopsy), yr	349 (100)	17 (1128)	18 (11–36)	16 (11–25)	14 (10–22)	16 (11–27)
Interval onset–baseline (biopsy), mo	346 (99)	5.6 (1.4–24)	4.7 (0.8–20.7)	6.5 (1.8–24.1)	7.1 (1.7–33.4)	7.3 (2–26.8)
Clinical presentation at onset, <i>n</i> (%)						
Hematuria	340 (97)	288 (85)	110 (82)	178 (87)	33 (85)	121 (88)
Nephrotic-range proteinuria	279 (80)	125 (45)	63 (58)	62 (37) ^b	16 (46)	38 (35)
eGFR (ml/min per 1.73m ²)	217 (62)	83 (61–103)	83 (58–103)	81 (61–102)	93 (67–113)	81 (57–102)
Arterial hypertension	339 (97)	141 (42)	65 (48)	76 (37)	14 (36)	52 (38)
Edema	342 (98)	133 (39)	74 (53)	59 (29) ^b	15 (39)	38 (28)
Complement biochemical and genetic profile, <i>n</i> (%)						
Low serum C3 at first measurement	347 (99)	293 (84)	114 (81)	179 (87)	37 (93)	119 (86)
Low serum C4 at first measurement	333 (95)	99 (30)	49 (36)	50 (25)	14 (35)	33 (25)
sC5b-9 at first measurement (ng/ml)	323 (93)	377 (224.5–1394)	358.5 (248.2–1441.2)	396 (209–1357)	286 (199.5–622.2)	490 (209–1604.2) ^c
Positive C3NeFs at first measurement	335 (96)	130 (39)	58 (41)	72 (37)	30 (75)	38 (28) ^c
Rare functional variant in complement gene	346 (99)	53 (15)	18 (13)	35 (17)	5 (13)	26 (19)
Rare variant gene, <i>n</i> (%)						
CFH		17 (32)	6 (33)	11 (31)	2 (40)	8 (31)
CFI		6 (11)	0	6 (17)	1 (20)	4 (15)
C3		17 (32)	5 (28)	12 (34)	1 (20)	11 (42)
CFB		4 (8)	44 (22)	0	0	0
THBD		6 (11)	1 (6)	5 (14)	1 (20)	2 (8)
MCP		2 (2)	1 (6)	0	0	0
Structural variant		2 (4)	1 (6)	1 (3)	0	1 (4)
Clinical parameters at baseline (biopsy)						
Proteinuria (g/24 h)	313 (90)	3 (1.1–5.3)	4 (1.9–7.2)	2.3 (0.8–4.6) ^b	2.9 (1.2–6.1)	2.2 (0.7–4.3)
eGFR (ml/min per 1.73 m ²)	317 (91)	84 (57–109)	77 (54–106)	92 (62–111)	102 (71–120)	93 (63–108.9)
Serum albumin (g/dl)	254 (73)	3.3 (2.6–3.9)	2.9 (2.3–3.6)	3.5 (2.9–4) ^b	3.1 (2.2–3.8)	3.6 (3–4.1) ^c
Histological parameters						
Fraction of sclerotic glomeruli, mean (±SD)	337 (97)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Fraction of crescents, mean (±SD)	334 (96)	0.1 (0.2)	0.1 (0.2)	0 (0.1)	0.1 (0.2)	0 (0.1)
Degree of mesangial proliferation (0–3)	339 (97)	2 (1–3)	2 (2–3)	2 (1–2.6) ^b	2 (1–2.5)	2 (1–3)
Degree of endocapillary proliferation (0–3)	333 (95)	1 (0–2)	1.5 (0–2)	1 (0–2)	0.3 (0–2)	1 (0–2)
Degree of interstitial inflammation (0–3)	339 (97)	0.5 (0–1)	1 (0–1)	0.1 (0–1)	0.3 (0–1.1)	0 (0–1)
Degree of interstitial fibrosis (0–3)	335 (96)	0 (0–1)	0.1 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Degree of arteriolar sclerosis (0–3)	330 (95)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
Clinical parameters at 1 yr from baseline						
Proteinuria at 1 yr (g/24 h)	220 (63)	0.9 (0.3–2.6)	1.3 (0.4–4)	0.7 (0.2–1.9) ^b	1.6 (0.2–2.7)	0.6 (0.2–1.6) ^c
Delta proteinuria at 1 yr	208 (60)	−0.6 (−0.8 to −0.2)	−0.6 (−0.8 to −0.1)	−0.6 (−0.8 to −0.2)	−0.6 (−0.8 to −0.2)	−0.6 (−0.8 to −0.2)
eGFR at 1 yr (ml/min per 1.73 m ²)	217 (62)	97 (73–113)	91 (67–110)	101 (80–119)	104 (86–119)	102 (83–121)
Outcome						
eGFR at last follow-up (ml/min per 1.73 m ²)	246 (70)	99 (70–118)	97 (64–114)	100 (72–121)	103 (84–123)	100 (72–121)

Table 1. (Continued)

Cohort Characteristics	Patients with Available Data, <i>n</i> (%)	Primary MPGN, all (<i>n</i> =349)	IC-MPGN (<i>n</i> =141)	C3G ^a (<i>n</i> =208)	DDD (<i>n</i> =40)	C3GN (<i>n</i> =140)
ESKD, <i>n</i> (%)	347 (99)	89 (26)	41 (29)	48 (23)	11 (28)	31 (22)
Death, <i>n</i> (%)	349 (100)	11 (3)	5 (4)	6 (3)	2 (5)	3 (2)
Follow-up from baseline (biopsy), mo	347 (99)	59.1 (25.1–107.7)	61.2 (36.6–107.7)	57.5 (20.1–105.4)	92 (29.6–149.1)	50.2 (19.3–102.6) ^c
Treatment, <i>n</i> (%)						
RAAS inhibition before/in first year from baseline	339 (97)	247 (73)	103 (76)	144 (71)	29 (73)	95 (70)
Immunosuppression before/in first year from baseline	343 (98)	246 (72)	112 (81)	134 (65) ^b	22 (56)	88 (64)
Corticosteroids only	343 (98)	117 (34)	49 (36)	68 (33)	15 (39)	41 (30)
Corticosteroids and MMF	343 (98)	64 (19)	25 (18)	39 (19)	0	29 (21) ^c
Corticosteroids and others	343 (98)	64 (19)	38 (28)	26 (13) ^b	7 (18)	17 (12)
Complement inhibition at any time	348 (100)	55 (16)	22 (16)	33 (16)	9 (23)	23 (17)
Complement inhibition at any time excluding patients with follow-up ending before 2010	327 (94)	54 (17)	22 (17)	32 (16)	8 (23)	23 (17)

Characteristics of patients categorized by histological diagnosis are described and compared (all, immune complex-mediated membranoproliferative GN versus C3 glomerulopathy and dense deposit disease versus C3GN). C3, complement component 3; C3G, immunofluorescence-based histological diagnosis of C3 glomerulopathy; C3GN, electron microscopy-based histological diagnosis of C3 glomerulonephritis; C3Nefs, C3 nephritic factors; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; DDD, electron microscopy-based histological diagnosis of dense deposit disease; IC-MPGN, immunofluorescence-based histological diagnosis of immune complex-mediated membranoproliferative GN; MCP, membrane cofactor protein; MMF, mycophenolate mofetil; RAAS, renin-angiotensin-aldosterone system; THBD, thrombomodulin.

Quantitative variables are expressed as medians with interquartile range unless otherwise specified. Means are presented with SD.

Interval onset—baseline, time (months) from disease onset to first diagnostic biopsy. Hematuria: microscopic or macroscopic. Nephrotic-range proteinuria: ≥ 3.5 g/24 hours, 3+ or ≥ 300 mg/dl by dipstick. eGFR: calculated using the full age spectrum equation (Pottel *et al.*, 2016; see [Supplemental References](#)). Arterial hypertension: as reported by the referring physician. Low serum C3: <90 mg/dl. Low serum C4: <16 mg/dl. sC5b9, soluble terminal complement complex (normal range: 140–280 ng/ml). Rare functional variant: missense, nonsense, splicing, frameshift, ins/del, with maximum minor allelic frequency ≤ 0.001 and combined annotation dependent depletion pathogenic score ≥ 10 . Structural variants: multiplex ligation-dependent probe amplification was used to evaluate the presence of novel or rare copy number variations in *CFH*, *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2*, and *CFHR5* genes. Twenty-four-hour proteinuria: measured using a 24 hour urine sample when available or estimated from a random spot urine using Hogan equation (Hogan *et al.*, 2016; see [Supplemental References](#)). Proteinuria at 1 year: proteinuria values between 6 and 18 months from baseline (time of first diagnostic biopsy). ESKD: defined as dialysis, preemptive transplantation or eGFR <15 ml/min per 1.73 m² at last available follow-up. Fraction of sclerotic glomeruli includes both globally and segmentally sclerotic glomeruli. Fraction of crescents includes all ages of crescents (cellular, fibrocellular and fibrous). Histological score on light microscopy: Mesangial and endocapillary proliferation (hypercellularity) were graded on a scale from 0 to 3: absent (0), trace (0.5), mild (1–1.5), moderate (2–2.5), and severe (3) corresponding to 0%, 1%–9%, 10%–25%, 26%–50%, $>50\%$ involvement of sampled glomeruli, respectively. Interstitial inflammation and interstitial fibrosis were graded on a scale from 0 to 3: absent (0), trace (0.5), mild (1–1.5), moderate (2–2.5), and severe (3) corresponding to 0%, 1%–9%, 10%–25%, 26%–50%, $>50\%$ involvement of cortical tubulointerstitial area, respectively. Arteriolar sclerosis was graded on a scale from 0 to 3 based on arteriolar intimal thickening: absent (0), mild (1), moderate (2), or severe (3). Delta proteinuria at 1 year: change in 24 hours proteinuria from baseline (time of first diagnostic biopsy) to 1 year, calculated as the ratio of (baseline 24-hour proteinuria [g/24 hours]–1-year 24-hour proteinuria [g/24 hours]) to baseline 24-hour proteinuria (g/24 hours). Follow-up from baseline: time (months) from first diagnostic biopsy to ESKD or last available follow-up. Immunosuppression: mycophenolate mofetil, mycophenolate mofetil; others: calcineurin inhibitors, cyclophosphamide, azathioprine.

^aTwenty-eight of the 208 patients with C3 glomerulopathy did not have available electron microscopy.

^bStatistically significant difference between IC-MPGN and C3G cases.

^cStatistically significant difference between DDD and C3GN cases.

Table 2. Multivariable model of the association between 1-year proteinuria and composite endpoint

Variables	HR	95% CI	P Value
1-yr proteinuria (g/24 h)	1.33 ^a	1.12 to 1.57 ^a	<0.001 ^a
IC-MPGN diagnosis	0.83	0.25 to 2.76	0.76
Age at onset	1.00	0.96 to 1.05	0.88
Female sex	0.29 ^a	0.09 to 0.97 ^a	0.04 ^a
C3NeF-positivity	0.55	0.19 to 1.63	0.28
Genetic predisposition	4.95	0.94 to 26.02	0.06
Hypertension at onset	1.47	0.43 to 5.03	0.53
Edema at onset	3.53	0.74 to 16.73	0.11
Interval onset—baseline (biopsy)	1.06	0.96 to 1.17	0.27
Arteriolar sclerosis (LM)	0.96	0.38 to 2.41	0.92
Crescents (LM)	0.02	0 to 1	0.05
Endocapillary proliferation (LM)	0.77	0.47 to 1.27	0.31
Interstitial fibrosis (LM)	1.07	0.42 to 2.68	0.89
Interstitial inflammation (LM)	1.65	0.73 to 3.73	0.23
Mesangial proliferation (LM)	0.83	0.47 to 1.46	0.52
Glomerular sclerosis (LM)	294.33 ^a	2.65 to 32690.37 ^a	0.02 ^a
RAAS inhibitors	0.07	0 to 1.1	0.06
RAAS inhibitors and steroids	0.30	0.03 to 3.04	0.31
RAAS inhibitors, steroids and MMF	0.23	0.01 to 3.94	0.31
RAAS inhibitors, steroids and other IS	0.61	0.06 to 6.2	0.68
IS only	0.69	0.09 to 5.42	0.72

1-year proteinuria (g/24 h), proteinuria levels measured at 1 year from baseline (time of first diagnostic biopsy); C3NeF-positivity, positive C3 nephritic factors at first measurement; CI, confidence interval; genetic predisposition, presence of rare functional variants in complement genes or positive family history for complement-mediated diseases; HR, hazard ratio; IC-MPGN, histological diagnosis of immune complex-mediated membranoproliferative GN; Interval onset—baseline, time (months) from disease onset to first diagnostic biopsy; IS, immunosuppressive; IS only, any type of immunosuppressive agents and no renin-angiotensin-aldosterone system inhibitors; LM, light microscopy; MMF, mycophenolate mofetil; RAAS, therapy with renin-angiotensin-aldosterone system inhibitors.

^aStatistically significant parameters.

Most patients were on renin-angiotensin-aldosterone system inhibitors (73%) and immunosuppressants (72%) before or during the first year after their biopsy. More patients with IC-MPGN than C3G (81% versus 65%, $P = 0.002$) and more with pediatric onset (78% versus 62%, $P = 0.001$) were on immunosuppressants. Most of them were given corticosteroids only (34%), while a minority (19%) received corticosteroids combined with mycophenolate mofetil or other immunosuppressive agents. Approximately 16% of patients with follow-up extending beyond 2010—when eculizumab and, subsequently, other complement inhibitors started to become available—received a course with a complement inhibitor, with a significantly higher proportion in the pediatric population (21% versus 9%, $P = 0.01$; Table 1 and Supplemental Table 1).

Association between Proteinuria and Long-Term Kidney Outcomes

Forty-nine out of 349 patients were excluded from the analyses because of insufficient follow-up. Patients with missing data for any variables required in a specific analysis were excluded from that analysis, resulting in varying sample size across analyses (Figure 1). At multivariable analysis, proteinuria levels at 1 year from baseline were significantly associated with the risk of progression to the composite endpoint. Each 1-g increase in 1-year proteinuria levels, *ceteris paribus*, was associated with a 33% higher risk of progression. Among considered covariates, male sex and higher proportion of sclerotic glomeruli seemed to be independently associated with an increased risk of

progression to the composite endpoint (Table 2, $n=165$). In line with this, patients who reached the composite endpoint had significantly higher proteinuria at 1 year compared with those who did not (Figure 2A, $n=192$). The same results were observed when data from patients with C3G and IC-MPGN were analyzed separately (Supplemental Figure 1A, $n=192$). Consistently, we found that levels of proteinuria at 1 year negatively correlated with eGFR values at the last available follow-up.

In the univariable Cox regression, we found that a 1-year proteinuria ≥ 1 g/24 hours was associated with a higher risk of reaching the composite endpoint as compared with a 1-year proteinuria < 1 g/24 hours (Supplemental Figure 2A, $n=200$). Accordingly, Kaplan–Meier analysis of ESKD-free survival at 10 years stratified by 1-year proteinuria showed significantly better kidney survival in patients with 1-year proteinuria < 1 g/24 hours compared with those with proteinuria ≥ 1 g/24 hours ($P = 0.02$; Figure 3, $n=205$).

In the multivariable model of the change in proteinuria from baseline to 1 year, no association was found between the 24-hour proteinuria changes and the composite endpoint (Table 3, $n=158$). Similarly, proteinuria changes at 1 year did not differ between patients with or without the composite endpoint, either in the entire cohort or in IF-based histological subgroups (Figure 2B and Supplemental Figure 1B, $n=182$). Univariable Cox regression categorizing patients into five groups according to proteinuria changes did not show any association between changes in proteinuria and the composite endpoint (Supplemental Figure 2B, $n=182$).

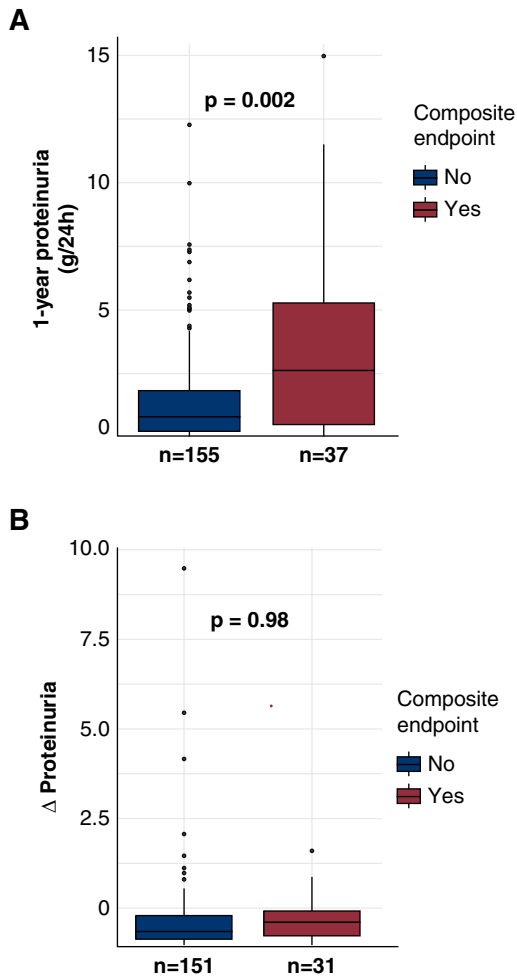


Figure 2. Association between proteinuria and composite endpoint. (A) One-year proteinuria in patients with (red) and without (blue) composite endpoint ($n=192$). (B) Changes in 24-hour proteinuria from baseline to 1 year in patients with (red) and without (blue) composite endpoint ($n=182$). Δ , change in 24-hour proteinuria from baseline to 1 year, calculated as the ratio of (baseline 24-hour proteinuria [g/24 hours]–1-year 24-hour proteinuria [g/24 hours]) to baseline 24-hour proteinuria (g/24 hours).

Other Associations with Long-Term Kidney Outcomes

In the multivariable analysis, eGFR at 1 year from baseline was inversely associated with the composite endpoint. Male sex and presence of edema at onset were also associated with a higher risk of progression to the composite endpoint (Table 4, $n=162$). Consistently, patients who reached the composite endpoint had significantly lower eGFR at 1 year compared with those who did not, both in the entire cohort and in IF-based histological subgroups (Figure 4 and Supplemental Figure 3, $n=188$).

The Kaplan–Meier survival analysis, stratified by age at onset, showed that 10-year ESKD-free survival was highest in patients with onset age below 12 years (86%; 95% confidence interval [CI], 76% to 96%) followed by those with adolescence onset (78%; 95% CI, 66% to 93%). Patients with adult onset (18 years or older) had the lowest ESKD-free survival (53%; 95% CI, 42% to 66%; Figure 5A, $n=330$).

When stratifying the Kaplan–Meier curve by diagnosis, the kidney survival at 10 years did not statistically differ across IF-based histological subtypes (Figure 5B, $n=332$). We could not find any significant differences when we also stratified patients by EM-based diagnosis (Supplemental Figure 4, $n=299$).

The 10-year ESKD-free survival was similar between patients with or without genetic susceptibility—defined as carrying rare functional variants in complement genes and/or having a positive family history of complement-mediated diseases (Supplemental Figure 5, $n=330$).

Discussion

In this retrospective study, we describe clinical, histological, and biochemical features of a large cohort of 349 children and adults with primary C3G and IC-MPGN, providing novel and robust insights into the natural history of the disease and identifying associations of long-term kidney outcomes. In particular, we found that (1) patients with primary C3G and IC-MPGN share most baseline and longitudinal features; (2) progression to ESKD was independent of the histological category; (3) proteinuria levels under 1 g/24 hours at 1 year from diagnosis were significantly associated with lower risk of kidney outcomes; (4) pediatric onset was associated with better kidney survival.

Similarly to several cohorts, most baseline and longitudinal characteristics in patients with C3G and IC-MPGN were similar.^{23,25,30} However, nephrotic-range proteinuria was more frequent at disease onset in patients with IC-MPGN as compared with those with C3G. Consistently, at time of biopsy, median proteinuria was significantly higher and serum albumin lower in patients with IC-MPGN. This finding confirms previous data by other researchers, suggesting a greater degree of disease activity associated with Ig deposition in IC-MPGN and possibly explaining the greater burden of immunosuppression therapy in our IC-MPGN cohort.^{5,31}

Regarding complement system profiling, our results showed the presence of rare variants in complement genes in around 15% of cases across histological categories, similarly to other cohorts.^{5,32,33} Unsurprisingly, most of the patients presented with low C3, while only about a third had low C4 levels, pointing to the predominant activation of the alternative complement pathway. Notably, low C3 and low C4 are more frequent in children than adults, along with higher sC5b9 levels, possibly reflecting the higher frequency of infectious triggers at onset activating both classical and alternative pathways.³⁴ The lower levels of sC5b-9 and higher prevalence of low levels of serum C3 in DDD cases, although nonsignificant, suggest different pathophysiology of DDD from IC-MPGN and C3GN, the former characterized by more frequent proximal, rather than terminal activation of the complement cascade. The significant higher rate of C3NeF-positivity in these patients highlights the key role of C3 convertase stabilization in this condition.^{2,5} A high proportion of C3NeF-positivity was also found in patients with IC-MPGN, consistent with accurate exclusion of secondary cases and with previous findings from a French cohort.⁵ Given the specificity of our C3NeF assay for the stabilization of the alternative

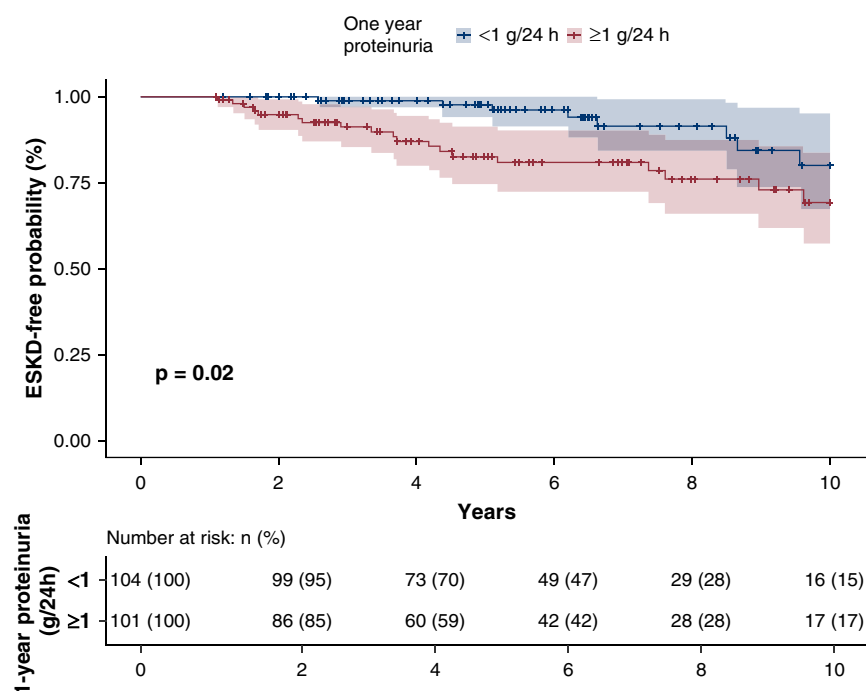


Figure 3. Kaplan–Meier curve for kidney survival stratified by 1-year proteinuria levels below 1 versus 1 g/24 hours or higher ($n=205$). Patients with available clinical information were censored at 10 years from onset or at the event.

Table 3. Multivariable model of the association between proteinuria reduction at 1 year and composite endpoint

Variables	HR	95% CI	P Value
Delta proteinuria at 1 yr	1.09	0.92 to 0.59	0.78
Age at onset	1.00	1 to 0.95	0.91
Female sex	0.31	3.28 to 0.08	0.08
C3NeF-positivity	0.55	1.8 to 0.16	0.35
Genetic predisposition	5.02	0.2 to 0.92	0.06
IC-MPGN diagnosis	1.07	0.94 to 0.32	0.91
Hypertension at onset	1.57	0.64 to 0.48	0.46
Edema at onset	6.63 ^a	0.15 to 1.09 ^a	0.04 ^a
Interval onset—baseline (biopsy)	1.03	0.97 to 0.93	0.55
Arteriolar sclerosis (LM)	0.83	1.2 to 0.29	0.73
Crescents (LM)	0.15	6.66 to 0	0.44
Endocapillary proliferation (LM)	0.77	1.3 to 0.43	0.39
Interstitial fibrosis (LM)	1.29	0.77 to 0.56	0.55
Interstitial inflammation (LM)	1.23	0.81 to 0.56	0.57
Mesangial proliferation (LM)	0.97	1.03 to 0.55	0.91
Glomerular sclerosis (LM)	418.01 ^a	3.31 to 52793.411 ^a	0.01 ^a
RAAS inhibitors	0.18	5.6 to 0.02	0.17
RAAS inhibitors and steroids	0.22	4.58 to 0.02	0.25
RAAS inhibitors, steroids and MMF	0.20	4.92 to 0.01	0.27
RAAS inhibitors, steroids and other IS	0.38	2.61 to 0.02	0.50
IS alone	0.52	1.91 to 0.06	0.57

Delta proteinuria at 1 year: change in 24-hour proteinuria from baseline (time of first diagnostic biopsy) to 1 year, calculated as the ratio of (baseline 24-hours proteinuria [g/24 hours]–1-year 24-hour proteinuria [g/24 hours]) to baseline 24-hour proteinuria (g/24 hours). C3NeF-positivity, positive C3 nephritic factors at first measurement; CI, confidence interval; genetic predisposition, presence of rare functional variants in complement genes or positive family history for complement-mediated diseases; HR, hazard ratio; IC-MPGN, histological diagnosis of immune complex-mediated membranoproliferative GN; interval onset—baseline, time (months) from disease onset to first diagnostic biopsy; IS, immunosuppressive; IS only, any type of immunosuppressive agents and no renin-angiotensin-aldosterone system inhibitors; LM, light microscopy; MMF, mycophenolate mofetil; RAAS, therapy with renin-angiotensin-aldosterone system inhibitors.

^aStatistically significant parameters.

Table 4. Multivariable model of the association between 1-year eGFR and composite endpoint

Variables	HR	95% CI	P Value
1-yr eGFR (ml/min per 1.73 m ²)	0.97 ^a	0.95 to 1 ^a	0.03 ^a
Age at onset	1.01	0.97 to 1.05	0.60
Female sex	0.19 ^a	0.06 to 0.62 ^a	0.01 ^a
C3NeF-positivity	0.74	0.27 to 2.05	0.57
Genetic predisposition	3.01	0.95 to 9.5	0.06
IC-MPGN diagnosis	0.99	0.35 to 2.79	0.99
Hypertension at onset	1.47	0.52 to 4.16	0.46
Edema at onset	3.52 ^a	1.05 to 11.78 ^a	0.04 ^a
Interval onset—baseline (biopsy)	0.99	0.85 to 1.15	0.90
Arteriolar sclerosis (LM)	0.72	0.33 to 1.59	0.42
Crescents (LM)	0.02	0 to 5.18	0.17
Endocapillary proliferation (LM)	0.87	0.55 to 1.36	0.54
Interstitial fibrosis (LM)	1.17	0.54 to 2.56	0.69
Interstitial inflammation (LM)	0.73	0.33 to 1.6	0.43
Mesangial proliferation (LM)	1.00	0.64 to 1.54	0.99
Glomerular sclerosis (LM)	24.26	0.74 to 794.62	0.07
RAAS inhibitors	1.06	0.15 to 7.58	0.95
RAAS inhibitors and steroids	1.08	0.19 to 6.2	0.93
RAAS inhibitors, steroids and MMF	1.19	0.11 to 13.48	0.89
RAAS inhibitors, steroids and other IS	3.06	0.38 to 24.5	0.29
IS alone	2.06	0.39 to 10.71	0.39

1-year eGFR, eGFR (ml/min per 1.73 m²) at 1 year from baseline (time of first diagnostic biopsy); C3NeF-positivity, positive for the C3 nephritic factors at first measurement; CI, confidence interval; genetic predisposition, presence of rare functional variants in complement genes or positive family history for complement-mediated diseases; HR, hazard ratio; IC-MPGN, histological diagnosis of immune complex-mediated membranoproliferative GN; interval onset—baseline, time (months) from disease onset to first diagnostic biopsy; IS, immunosuppressive; IS only, any type of immunosuppressive agents and no renin-angiotensin-aldosterone system inhibitors; LM, light microscopy; MMF, mycophenolate mofetil; RAAS, therapy with renin-angiotensin-aldosterone system inhibitors.

^aStatistically significant parameters.

pathway C3 convertase,³ these data suggest a role of the alternative pathway C3 convertase stabilization also in primary IC-MPGN, further underlying an overlapping pathogenesis with C3G.

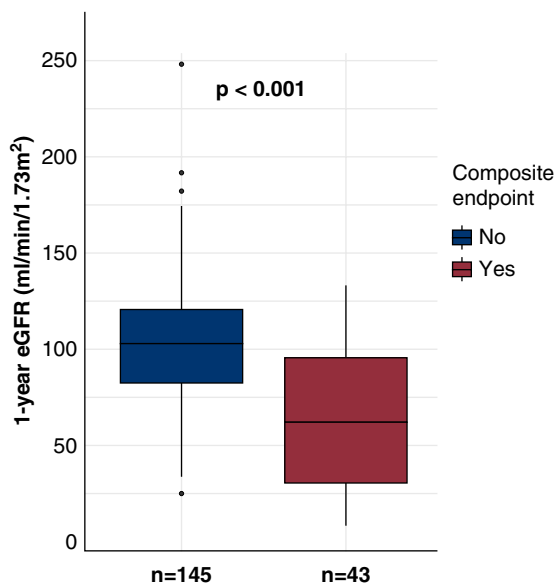


Figure 4. Association between 1-year eGFR and composite endpoint (n=188). Values of eGFR (ml/min per 1.73 m²) at 1 year from baseline in patients with (red) and without (blue) composite endpoint.

Almost 30% of our population progressed to ESKD over a median follow-up of 5 years from diagnosis, similarly to other cohorts.^{11,22,23,32} Notably, ESKD rate was independent of the histological category, as confirmed by Kaplan–Meier analyses showing similar 10-year kidney survival across histological subtypes. Consistently, IF-based diagnosis had no effect on the relationship between proteinuria or eGFR and the composite endpoint. This finding is in line with recent data from the RaDaR cohort²³ and is particularly remarkable given the large size of our cohort and the conflicting data in the literature on the prognostic implications of histological diagnosis. In some cohorts, patients with DDD and C3GN shared similar outcomes.^{11,35} Others found DDD to have a worse prognosis than IC-MPGN or C3GN.^{5,32,36} Lomax-Browne *et al.* reported lower ESKD-free survival for both C3GN and DDD compared with IC-MPGN.²⁶

Another key finding of our study was that higher proteinuria at 1 year after diagnosis was significantly associated with a higher risk of adverse kidney outcomes. This association was confirmed across multiple sensitivity analyses and using various proteinuria thresholds. However, changes in proteinuria from baseline to 1-year follow-up did not correlate with kidney outcomes. These findings challenge the approach in recent interventional trials that rely on proteinuria reduction over time as a reliable surrogate predictor of improved long-term outcomes. Nonetheless, inconsistent results regarding the effect of changes in proteinuria on kidney survival have been reported in literature. In the RaDaR study, a 50% UPCR reduction at 12 months was associated with a lower rate of ESKD, but

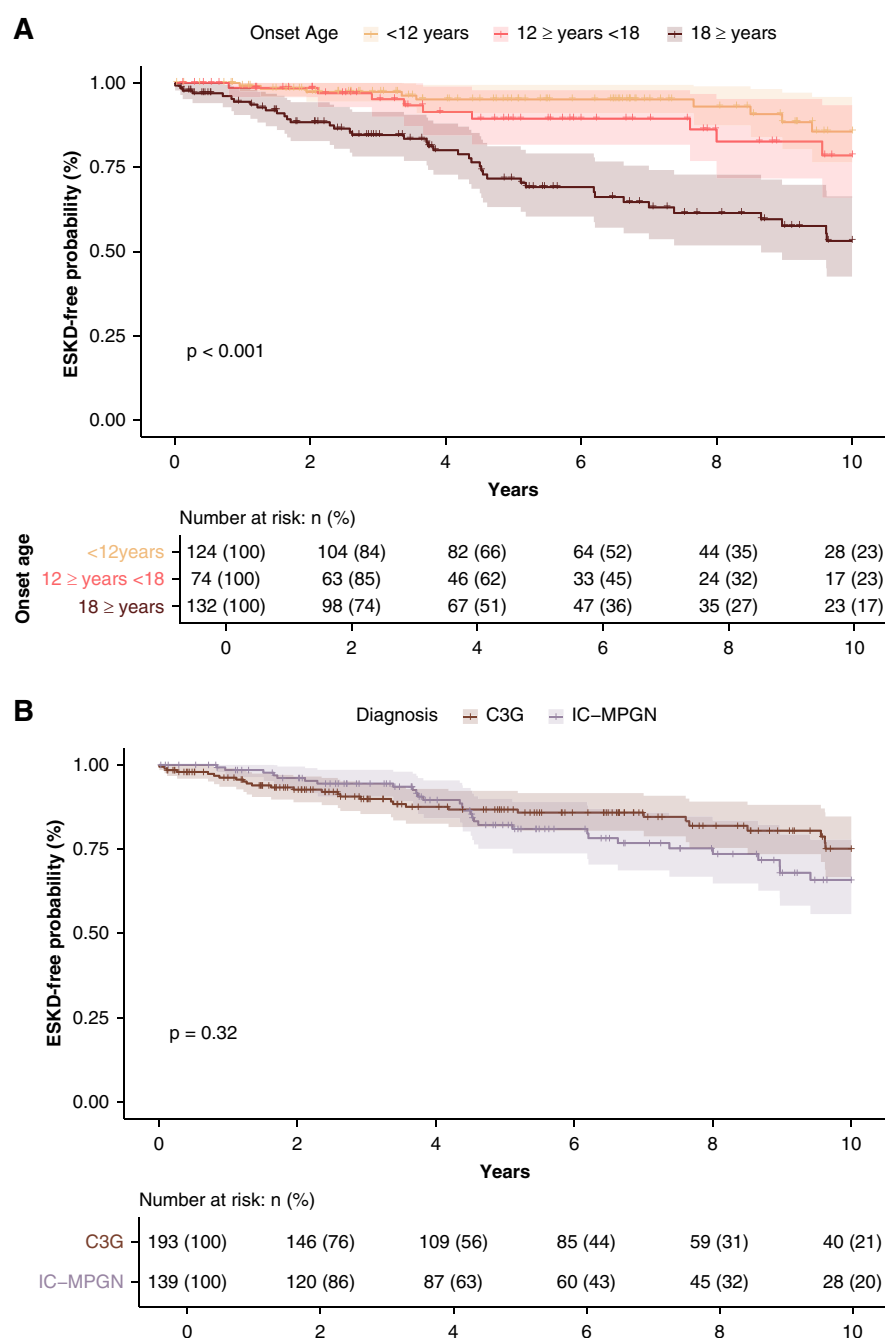


Figure 5. Kaplan-Meier curves for kidney survival stratified by age of onset and by immunofluorescence-based histological diagnosis. Kaplan-Meier curves for kidney survival stratified by age of onset (A, $n=330$) and by IF-based histological diagnosis (B, $n=332$). Patients with available clinical information were censored at 10 years from onset or at the event. Patients with ESKD before baseline were removed from the analyses. Age classes: younger than 12 years, patients with pediatric onset; 12 to younger than 18 years, patients with onset in adolescence; 18 years or older, patients with onset in adulthood.

achieving a threshold UPCR under 100 mg/mol was particularly strongly associated with lower risk.²³ Caravaca-Fontán *et al.* showed a lower risk of kidney failure in patients with $\geq 50\%$ proteinuria reduction from baseline, with better kidney outcomes in those with time-averaged proteinuria values <1 g/24 hours, similarly to a recent multicohort study.^{22,25} By contrast, in 75 patients with IC-MPGN and C3G with over 2 years of follow-up, Lomax *et al.* showed that kidney survival did not differ between

patients who achieved a 50% proteinuria reduction and those who did not.²⁶ In our present work, consistent with previous studies demonstrating the association with post-treatment residual proteinuria *per se* in several cohorts of patients with proteinuric nephropathies,^{37–39} absolute proteinuria levels during follow-up reliably associated with long-term disease outcomes. This finding supports the possibility that lowering proteinuria below a specific threshold in the short term may result in a better kidney

prognosis than the extent of proteinuria reduction itself. Specifically, our analyses provide the rationale for targeting a 1-year proteinuria level below 1 g/24 hours as a minimal therapeutic goal in interventional trials in primary C3G/IC-MPGN. This aligns with a recent study in patients with C3G/IC-MPGN showing that, when proteinuria was modeled as a time-varying variable, the risk of kidney failure was higher with values above 1 g/24 hours.²⁵ Overall, our findings support the complementary use of proteinuria reduction and absolute levels of residual proteinuria as potential surrogate endpoints for disease progression in C3G and IC-MPGN.

Several studies have attempted to identify additional associations for kidney failure in patients with MPGN, including age at onset, kidney function, genetic predisposition, histological category, or parameters.^{11,25,26,32,35,39–41} In our study, the higher kidney survival in patients with pediatric onset aligns with findings from smaller pediatric cohorts.^{30,42,43} It may be speculated that earlier and more intensive treatment, as well as the absence of comorbidities in children compared to adults, could lead to a better prognosis. Conversely, adult-onset disease might reflect delayed diagnosis, which could be associated with more severe chronic and irreversible kidney morphological changes, as indicated by the more frequent chronic lesions in patients with adult onset.

When evaluating kidney function as an association with kidney outcomes, we observed that lower 1-year eGFR was significantly associated with a higher risk of disease progression, consistent with other studies.^{11,23}

Finally, although rare functional complement genetic variants or a family history of complement-associated diseases have been suggested to negatively affect kidney outcomes, our survival analysis showed no significant difference between individuals with a genetic predisposition and those without.

This study has several limitations. Its retrospective and observational design limits the ability to establish causality, especially because only a subset of patients had detailed longitudinal data available, and the 1-year time point included values recorded between 6 and 18 months from baseline. Because the cohort was multicentric, variations in biopsy timing and treatment patterns introduced heterogeneity that may have influenced outcomes. Proteinuria measurements were nonstandardized, making the results susceptible to random fluctuations. The limited follow-up period may have prevented our capacity to fully assess long-term kidney survival. Finally, the lack of racial and ethnical diversity in our cohort could potentially affect the generalizability of our findings.

Despite these limitations, our results from a large, well-characterized cohort of individuals with primary C3G/IC-MPGN and extensive complement profiling, provide valuable insights to inform clinical practice and guide the potential use of emerging complement inhibitors.

In conclusion, our findings highlight the overlapping features of primary C3G and IC-MPGN, underscore the importance of early diagnosis, and substantially contribute to the discussion about surrogate endpoints for long-term kidney outcomes. By demonstrating the prognostic value of residual proteinuria burden, our results suggest that absolute proteinuria thresholds may better capture the risk

of long-term kidney outcomes than the magnitude of proteinuria reduction.

These findings can inform the implementation of emerging complement-targeted therapies in clinical practice and support the integration of proteinuria level as a surrogate endpoint in interventional trials for primary C3G/IC-MPGN.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/CJN/C579>.

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Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent. This study includes clinical experimentation and complies with the Declaration of Helsinki.

Data Availability Statements

Original data generated for the study will be made available upon reasonable request to the corresponding author. Data Type: Aggregated Data, Health Care Data, Image Data, Observational Data, and Statistical Analysis Plan. Reason for Restricted Access: Partial restrictions to the data and the materials apply. Sharing individual participant data with third parties was not specifically included in the informed consent form for the study, and unrestricted sharing of this data may pose the threat of revealing participants' identities. To minimize this risk, individual participant data underlying the results reported in this article will be available upon request for 5 years following publication. Researchers shall submit a methodologically sound proposal to raredis@marionegri.it. To gain access, data requestors will need to sign a data access agreement and obtain the approval of the local ethics committee.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/CJN/C580>.

Supplemental Methods

Supplemental References

Supplemental Table 1. Cohort description by age at onset.

Supplemental Table 2. Clinical features of the 13 patients with rapid progression to ESKD.

Supplemental Figure 1. Association between proteinuria and composite endpoint by IF-based histological diagnosis.

Supplemental Figure 2. Forest plots of different 1-year proteinuria thresholds (A) and different degrees of changes in proteinuria at 1 year from baseline (B).

Supplemental Figure 3. Association between 1-year eGFR and composite endpoint by IF-based histological diagnosis.

Supplemental Figure 4. Kaplan–Meier curves for kidney survival stratified by EM-based histological diagnosis.

Supplemental Figure 5. Kaplan–Meier curve for kidney survival stratified by genetic predisposition.

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