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Comparative Analysis of Proteinuria and Longitudinal Outcomes in Immune Complex Membranoproliferative Glomerulonephritis and C3 Glomerulopathy

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Introduction: C3 glomerulopathy (C3G) and primary immune complex–mediated membranoproliferative glomerulonephritis (IC-MPGN) are rare diseases that share a similar pathogenesis; however, the prognostic significance of proteinuria reduction remains poorly characterized. This study compared the outcomes in C3G and IC-MPGN and assessed the impact of changes in proteinuria on kidney prognosis.

Methods: This retrospective, longitudinal, multicenter study used joint linear mixed-effects models to assess proteinuria trajectories, and Cox regression to evaluate their association with kidney failure. In addition, time-averaged proteinuria (TA-P) was calculated to determine its impact on kidney prognosis.

Results: The study included 149 patients: 98 with C3G (66%) and 51 with IC-MPGN (34%) with a median age of 35 (interquartile range [IQR]: 22–53) years. During a median follow-up of 65 (IQR: 32–114) months, 44 patients (30%) progressed to kidney failure without differences across C3G or IC-MPGN. A strong association was observed between longitudinal increase in proteinuria and the risk of kidney failure. In addition, a $\geq$ 50% proteinuria reduction over time was associated with a lower risk of kidney failure (hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.46–0.75, $P < 0.001$). Results were consistent in both C3G and IC-MPGN, and in those with baseline estimated glomerular filtration rate (eGFR) $\geq$ 30 ml/min per 1.73 m^2 and proteinuria $\geq$ 1 g/d. A $\geq$30% proteinuria reduction at 6 months or a $\geq$50% proteinuria reduction at 12 months were associated with a slower eGFR decline. Patients were categorized into 4 subgroups based on TA-P levels, with TA-P values $<$ 1 g/d indicating better kidney outcomes.

Conclusion: Proteinuria reduction was associated with improved kidney outcomes and slower eGFR decline in both C3G and IC-MPGN.

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C3G is an ultrarare glomerular disease driven by dysregulation of alternative complement pathway.[1,2] The estimated incidence ranges from 0.2 to 2 cases/million/yr, with a reported prevalence of 0.05 to 1.4 per 10,000 individuals.[3] This activation results in the deposition of C3 and its breakdown products, triggering inflammation and contributing

to the progressive deterioration of kidney function.[3] The current consensus definition is based on the identification of dominant C3 deposits in the immunofluorescence staining of kidney biopsy. When kidney biopsy specimens are evaluated using electron microscopy, 2 major histological subgroups are identified: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).[4,5] Although the clinical profiles of patients with C3GN and DDD may differ, this histological distinction has not yet been shown to have a significant impact on clinical outcomes.[6]

In recent years, seminal contributions in the field have demonstrated that complement dysregulation may also be involved in the pathogenesis of primary IC-MPGN, where C3 and Ig deposits of similar intensity may coexist.[7-9] This suggests that IC-MPGN may fall within the same disease spectrum as C3G and could potentially benefit from similar management approaches.[10,11] Indeed, several clinical trials investigating novel anticomplement therapies include both patients with C3G and those with IC-MPGN.[12]

Despite advances in the understanding of IC-MPGN, its natural history and predictors of long-term outcomes remain poorly characterized in the literature.[8,13-16] Given that kidney failure typically occurs late in the disease course, there is a clinical need to identify potential surrogate markers of progression. Although previous studies have shown an association between longitudinal changes in proteinuria and kidney outcomes in C3G,[17] the prognostic significance of proteinuria reduction over time in C3G and IC-MPGN has yielded discrepant results.[13] This variability may stem from significant heterogeneity in the clinical presentation and management approaches used with currently available therapies.

Therefore, the aims of this study were to analyze and compare the longitudinal outcomes of C3G and IC-MPGN in a large, multicenter cohortand to evaluate whether changes in proteinuria could serve as a surrogate marker for kidney failure in patients with these conditions.

METHODS

Study Patients

The patients included those diagnosed with C3G or IC-MPGN in native kidneys between 1991 and 2023 from 36 nephrology departments affiliated with the Spanish Group for the Study of Glomerular Diseases. The study included both pediatric and adult populations; however, the proportion of pediatric IC-MPGN cases was lower because of the reduced participation of pediatric nephrologists in case data collection.

C3G diagnosis required C3 staining on immunofluorescence to be at least 2 orders of magnitude greater than immunoglobulin staining. Patients were classified as having DDD when highly electron-dense intramembranous deposits were observed by electron microscopy, whereas those without such deposits were diagnosed with C3GN.

Primary IC-MPGN was defined as a membranoproliferative pattern of glomerular injury with significant immunoglobulin deposits without an identifiable secondary cause. All included patients with IC-MPGN had negative serology for hepatitis B and C, negative autoimmunity panel, negative serum and urine protein electrophoresis, and no active infection at the time of diagnosis.

Diagnoses from the pre-2012 period were reassessed using archived biopsy materials, clinical records, and laboratory data, to align with the updated classification criteria. Complementary profiles and histological findings were reviewed to distinguish C3G, DDD, and IC-MPGN. For cases lacking biopsy material, retrospective classification was based on documented clinical and laboratory data. Any cases in which the reclassification was uncertain owing to incomplete data were excluded.

The inclusion criteria required at least 4 consecutive measurements of eGFR and proteinuria during a follow-up period of $\geq$ 6 months. Patients were excluded if they had underlying monoclonal gammopathies, other autoimmune diseases, hepatitis B or C coinfection, missing longitudinal data, or a follow-up period $<$ 6 months.

The study was approved by the Institutional Review Board of Hospital Universitario 12 de Octubre (CEI16/266 and CEI23/460), and patients were enrolled after provided informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

The baseline and follow-up data were compiled from the medical records of all participating centers. Data on serum creatinine (determined by enzymatic assays), eGFR, serum albumin, serum C3 levels, and proteinuria were collected at baseline and at 1, 3, 6, 12, 24, and 60 months, and/or the last follow-up. Owing to the unavailability of albumin excretion data (or albumin-to-creatinine ratio) for all patients during follow-up, 24-hour total urine protein measurements were used at each time point. The kidney biopsy specimens were examined in the pathology departments of the participating hospitals. The degree of disease activity and chronicity were analyzed according to the previously published C3G histologic index,[6,18] either directly by the pathologist or

extracted from the original kidney biopsy report (Supplementary Methods). A subgroup of patients underwent testing for genetic variants and autoantibodies against complement components at Centro de Investigaciones Biológicas (Madrid, Spain), as previously described.[19]

Definitions and Outcomes

Baseline was defined as the time at which the diagnosis of C3G or IC-MPGN was made, and the follow-up period was defined as the interval between renal biopsy and the last outpatient visit or kidney failure.

Nephrotic syndrome was defined as proteinuria $>$ 3.5 g/d with a serum albumin level $<$ 3 g/dl. Nephritic syndrome is a combination of hematuria, non nephrotic proteinuria, hypertension, and impaired kidney function. Asymptomatic urinary abnormalities were defined as the presence of non nephrotic proteinuria and/or persistent microscopic hematuria with $>$ 5 erythrocytes per high-power field.

The main outcome was kidney failure, defined as an eGFR $<$ 15 ml/min per 1.73 m^2 by the Chronic Kidney Disease-Epidemiology Collaboration equation or the modified bedside Schwartz equation (for patients aged $<$ 18 years), the need for dialysis, or kidney transplantation. Secondary outcomes included complete remission defined as an eGFR $>$ 60 ml/min per 1.73 m^2, proteinuria $<$ 0.5g/24 h and no microscopic hematuria. Partial remission was defined as a proteinuria reduction $>$ 50% (and $<$ 3 g/d) plus stabilization ($\pm$ 25%) or improvement in kidney function. Although not universally standardized, these definitions have been utilized in previous cohort studies.[6,20] Relapse was defined as the reappearance of significant proteinuria ($>$ 1 g/d) and/or a 50% increase in proteinuria from the lowest recorded level after achieving remission, in the absence of any other underlying causes, and accompanied by microscopic hematuria and/or a decline in kidney function.

Statistical Analyses

This was a retrospective, longitudinal, multicenter, observational cohort study. Descriptive statistics are presented as mean $\pm$ SD or median and IQR for continuous variables, and as frequencies or percentages for categorical variables. Continuous variables were compared between the 2 groups using the unpaired *t* test or Mann-Whitney U test, as appropriate. For comparisons of continuous variables among more than 2 groups, 1-way analysis of variance or the Kruskal-Wallis's test was used, depending on the data distribution. The chi-square test or Fisher exact test was used to analyze categorical variables.

Estimates of the eGFR slope and changes in proteinuria over time were analyzed using linear mixed-effects models with random intercepts and random slopes. Positive and negative values for these parameters indicate increases and decreases over time, respectively.

A joint modeling approach was applied to simultaneously analyze the longitudinal evolution of proteinuria and the risk of progression to kidney failure. The model comprised 2 components: a linear mixed-effects model for the longitudinal outcome (proteinuria) and a Cox proportional hazards model for the time-to-event outcome (kidney failure). The fixed effects in the linear mixed-effect model included a natural spline over time, which allowed for a nonlinear trajectory of proteinuria over time. Random effects, including subject-specific random intercepts and slopes, were used to account for interindividual variability in proteinuria progression. The Cox sub model was adjusted for age, gender, histologic subtype, and categories of total activity and chronicity scores.[6,18] The results were presented as HR with 95% CIs. An extended joint model with a binary longitudinal outcome was further applied to analyze the association of a $\geq$ 50% proteinuria reduction with the risk of kidney failure. In addition, a censored version of the latter model was applied to analyze the association between a $\geq$ 30% proteinuria reduction within the first 6 months and a $\geq$ 50% proteinuria reduction at 12 months from diagnosis with the primary outcome. A small proportion of missing data ($<$ 5%) was handled using listwise deletion, and observations with missing values for the outcome or predictor variables were excluded from the analysis. The model was fitted using maximum likelihood estimation under the assumption that the data were missing completely at random. Sensitivity analyses, including multiple imputations missing at random yielded consistent results. The mixed-effects model accounted for individual variability through random effects, ensuring proper modeling of within-subject correlations.

Subject-specific longitudinal trajectory plots and locally weighted smoothing plots were used to represent changes in eGFR and proteinuria over time. Distributions of time to kidney failure were depicted by survival curves using the Kaplan-Meier method, and survival curves by clinical profile were compared using the log-rank test. To evaluate the nonlinear relationship between the percentage change in proteinuria and HR of kidney failure, flexible HR curves were plotted.

Propensity score matching analysis was further conducted to compare kidney survival across histologic subtypes, adjusting for baseline confounders, including age, eGFR, proteinuria, and total chronicity

Table 1. Baseline demographic and clinical characteristics according to histologic subtypes (C3GN vs DDD vs IC-MPGN)

Characteristics	Total (N = 149)	C3GN (n = 79)	DDD (n = 19)	IC-MPGN (n = 51)	P-value
Baseline					
Age, yrs	35 (22–53)	31 (19–49)	24 (14–47)	42 (32–55)	0.01
Age <18 yrs, *n* (%)	28 (19)	18 (23)	6 (32)	4 (8)	0.03
Gender, female *n* (%)	68 (46)	32 (41)	12 (63)	24 (47)	0.20
Clinical presentation					
Clinical presentation, *n* (%)					0.53
Nephrotic syndrome	62 (41)	28 (36)	9 (47)	25 (49)	
Nephritic syndrome	43 (29)	27 (34)	4 (21)	12 (23)	
Isolated non-nephrotic proteinuria	19 (13)	9 (11)	4 (21)	6 (12)	
Asymptomatic urinary abnormalities	25 (17)	15 (19)	2 (11)	8 (16)	
Serum creatinine, mg/dl	1.5 (0.8–2.5)	1.6 (0.8–3)	1 (0.5–1.6)	1.6 (0.8–2.3)	0.35
eGFR, ml/min per 1.73 m^2	55 (27–106)	55 (24–110)	70 (41–127)	52 (30–97)	0.14
Serum albumin, g/dl	3.2 (2.6–3.7)	3.2 (2.5–3.8)	3.2 (2.4–4)	3.2 (2.9–3.7)	0.85
Serum C3, mg/dl	74 (41–99)	71 (19–94)	59 (26–66)	87 (58–105)	0.003
Proteinuria, g/d	3 (1.7–5.6)	2.7 (1.5–4.7)	4 (2.1–5.2)	3.5 (2–6.4)	0.17
Histologic features					
Glomerulosclerosis, %	8 (0–25)	8 (0–28)	11 (0–20)	7 (0–24)	0.95
Any cellular/fibro cellular crescents, *n* (%)	37 (25)	19 (24)	3 (16)	15 (29)	0.49
Interstitial fibrosis / tubular atrophy, *n* (%)					0.42
< 10%	47 (31)	27 (34)	8 (42)	12 (23)	
11%–25%	61 (41)	33 (42)	5 (26)	23 (45)	
26%–50%	28 (19)	15 (19)	3 (16)	10 (20)	
> 50%	13 (9)	4 (5)	3 (16)	6 (12)	
C3G histologic index total activity score	7 (5–9)	7 (5–9)	7 (6–9)	7 (5–8)	0.47
C3G histologic index total chronicity score	2 (0–5)	2 (0–5)	2 (0–5)	3 (1–5)	0.47
Treatment					
RAS blockade, *n* (%)	133 (89)	71 (90)	17 (89)	45 (88)	0.49
Non-IS management, *n* (%)	10 (7)	7 (9)	2 (11)	1 (2)	0.24
Corticosteroids, *n* (%)	127 (85)	66 (84)	17 (90)	44 (86)	0.78
Mycophenolate mofetil, *n* (%)	83 (56)	46 (58)	7 (37)	30 (59)	0.21
Cyclophosphamide, *n* (%)	24 (16)	16 (20)	3 (16)	5 (10)	0.29
Rituximab, *n* (%)	36 (24)	12 (15)	2 (11)	22 (43)	0.001
Anti-C5, *n* (%)	10 (7)	6 (8)	3 (16)	1 (2)	0.11
Other combinations, *n* (%)	37 (25)	20 (25)	6 (32)	11 (22)	0.68
Outcomes					
Follow-up, mo	65 (32–114)	66 (44–107)	68 (38–123)	54 (21–134)	0.43
Slope of eGFR, ml/min per 1.73 m^2 per yr	−1.7 (−4.5; 1.1)	−1.1 (−3.4; 3.2)	−3.9 (−0.4; −7)	−1.7 (−0.2; −5.2)	0.02
Complete remission, *n* (%)	34 (23)	16 (20)	3 (16)	15 (29)	0.35
Remission (complete + partial), *n* (%)	82 (55)	47 (60)	9 (47)	26 (51)	0.49
Relapse after remission,[a] *n* (%)	26 (32)	16 (34)	2 (22)	8 (31)	0.78
Kidney failure, *n* (%)	44 (30)	20 (25)	7 (37)	17 (33)	0.47

C3G, complement 3 glomerulopathy; eGFR, estimated glomerular filtration rate; non-IS, non-immunosuppression; RAS, renin-angiotensin system.
[a]Only patients who had achieved any type of remission previously.

score. A 2:1 nearest-neighbor matching approach was applied with a caliper width of 0.19 without replacement, to ensure robust comparability between groups.

The predictive performance of the models was assessed using discrimination and calibration measures. In addition, 5-fold cross-validation was conducted to obtain a more accurate estimate of the predictive ability of changes in proteinuria over time.

TA-P was calculated by dividing the area under the curve of serial measurements by the total follow-up duration.

Analyses were performed using R software v.3.6.3, and the R packages "smoothHR," "pracma" and "JMBayes."[21] Two Markov Chain Monte Carlo chains of 30,000 iterations were performed, with the first 3000 discarded as burn-in to achieve convergence. A P value < 0.05 was considered to be significant.

RESULTS

Cohort Description and Outcomes

During the study period, data were retrieved from 175 patients diagnosed with C3G or IC-MPGN. Of these, 22 were excluded due to a lack of follow-up data, and 4 were excluded due to follow-up < 6 months (Supplementary Figure S1). The final study cohort included 149 patients: 79 (53%) with C3GN, 19 (13%) with DDD, and 51 (34%) with IC-MPGN. The median age at clinical diagnosis was

35 (IQR: 22–53) years (Table 1 and Supplementary Table S1). Baseline eGFR was 55 (IQR: 27–106) ml/min per 1.73 m^2, and baseline proteinuria was 3 (IQR: 1.7–5.6) g/d.

Corticosteroids were the most commonly prescribed treatment, administered to 127 patients (85%) at a median initial dose of 0.8 ± 0.3 mg/kg/d orally, either alone or in combination with mycophenolate mofetil (n = 83, 56%). The median time from histological diagnosis to treatment initiation was 7 (IQR: 3–21) days. Eculizumab was prescribed to 10 patients (7%) and rituximab use was significantly higher in patients with IC-MPGN (n = 22, 43%) than in the other subgroups.

During a median follow-up of 65 (IQR: 32–114) months, 44 patients (30%) progressed to kidney failure. The median eGFR slope in patients who reached kidney failure was −5.8 (IQR: −3 to −10) ml/min per 1.73 m^2 per year. There were no significant differences in the rates of kidney failure among the patients with C3GN, DDD, or IC-MPGN (Figure 1). To ensure robust and unbiased comparability between histological subgroups, a propensity score matching analysis was performed, which yielded similar findings (Supplementary Table S2, and Figures S2 and S3). The eGFR slope differed significantly across histologic subgroups (Table 1) and among those who progressed to kidney failure: C3GN showed a decline of −4.7 (IQR: −2 to −8.3) ml/min per 1.73m^2 per year, DDD exhibited a steeper decline of −7.1 (IQR: −5.5 to −13) ml/min per 1.73m^2 per year, and IC-MPGN had a decline of −6.2 ml/min per 1.73m^2 per year (IQR: −2 to −11).

Of the patients, 82 (55%) achieved some form of remission, with the majority experiencing partial remission (55%). However, 26 patients (32%) who had previously achieved remission experienced relapse during follow-up. No significant differences in remission rates were observed among the histological subgroups.

Longitudinal Change in Proteinuria and Kidney Failure Risk

The median number of proteinuria measurements per patient was 6 (IQR: 5–7), with a total of 887 observations. In Figure 2a and b, we depict the trajectories of

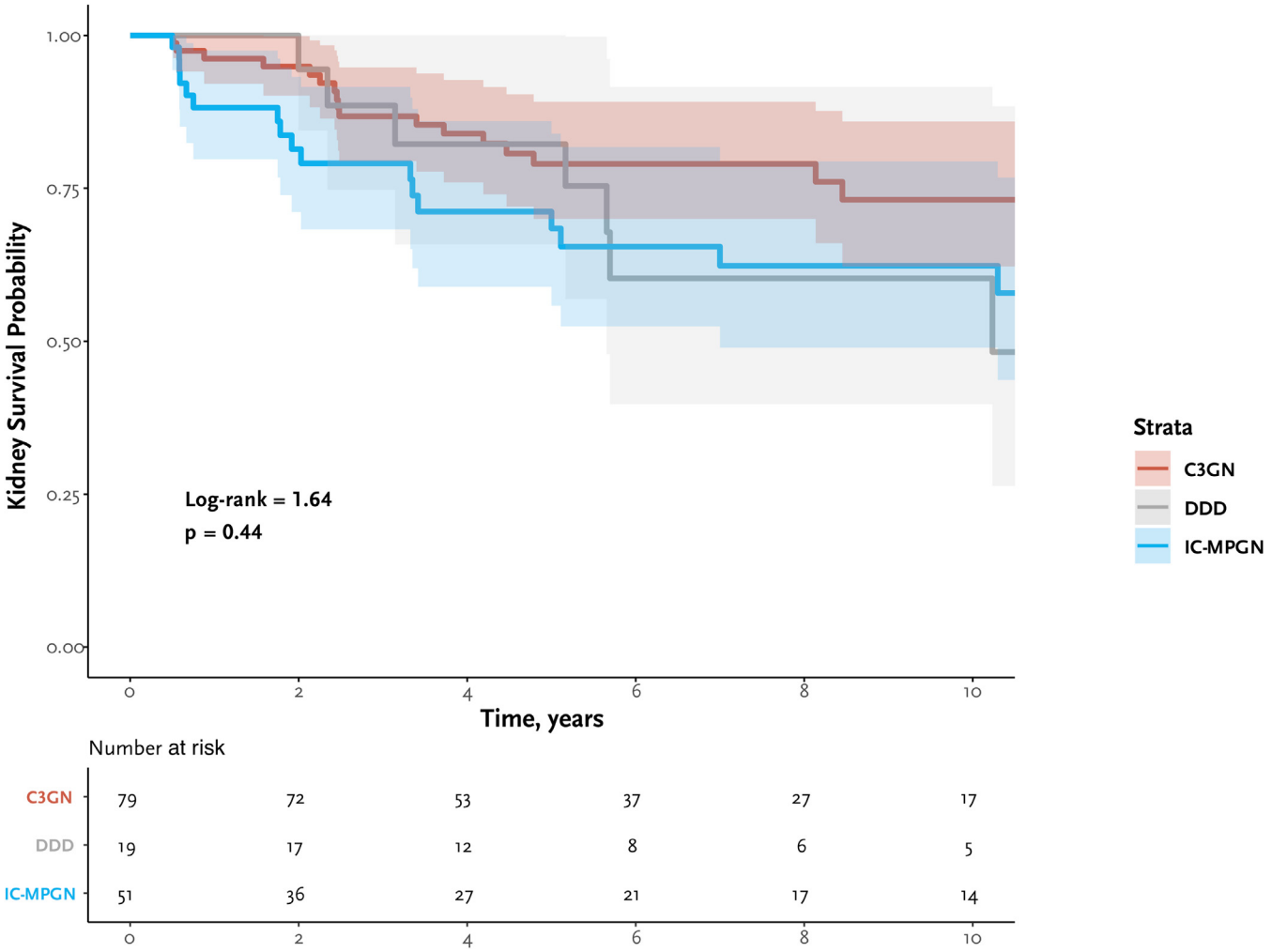

Figure 1. Kaplan-Meier curves for kidney survival according to histologic subgroups. C3GN, C3 glomerulonephritis; DDD, dense deposit disease; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

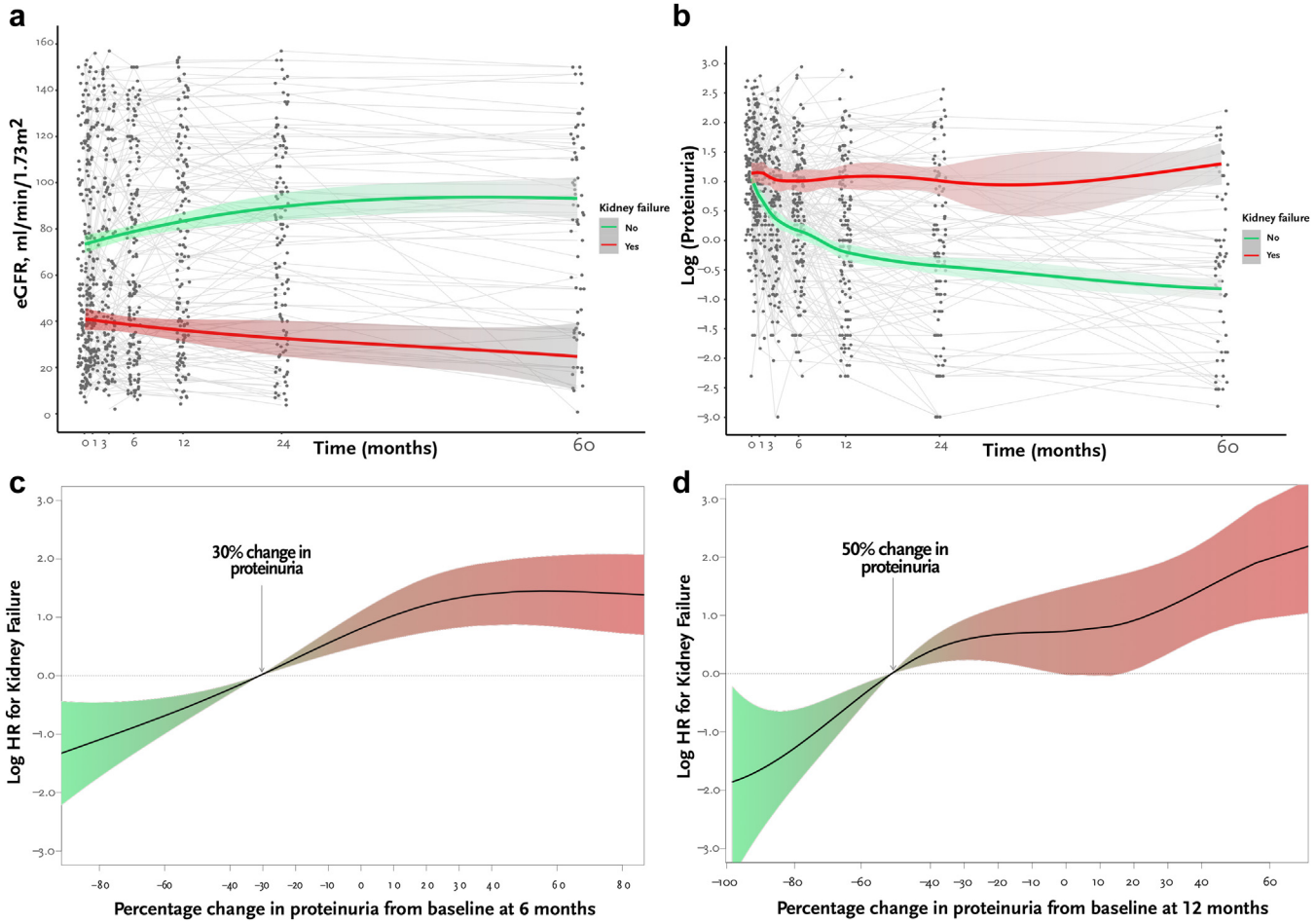

Figure 2. (a) Subject-specific longitudinal trajectories for eGFR, (b) subject-specific longitudinal trajectories for log-transformed 24-hour proteinuria, (c) relationship between percentage change in proteinuria at 6 months and log–hazard ratio for kidney failure, (d) relationship between percentage change in proteinuria at 12 months and log–hazard ratio for kidney failure. eGFR, estimated glomerular filtration rate; HR, hazard ratio.

eGFR and proteinuria according to kidney failure status.

To assess the association between longitudinal changes in proteinuria and the risk of kidney failure (as a continuous longitudinal outcome), the first joint model was fitted and adjusted for age, gender, baseline eGFR, histologic subtype (C3GN, DDD, or IC-MPGN), and total disease activity and chronicity scores (Table 2). Baseline eGFR and total chronicity score emerged as determinants of kidney failure. In addition, the model found a strong association between the longitudinal increase in proteinuria and the risk of this outcome, with each unit increase being associated with a 3.2-fold increase in the hazard of kidney failure (95% CI: 1.95–5.83, $P < 0.001$). To assess the discriminative capability of longitudinal changes in proteinuria, we focused on 6 to 60-month intervals. A receiver operating characteristic curve was constructed using the former joint model, yielding an area under the curve of 0.81, demonstrating a good discriminative ability for identifying patients who progress to kidney failure within a 5-year period. To better estimate the predictive ability of longitudinal changes in proteinuria, we implemented a 5-fold cross-validation technique. The average area under the curve across the 5 folds was 0.74, and the mean prediction error was 0.10. These metrics reflected an overall acceptable predictive performance in terms of discriminative ability and predictive accuracy.

The association between longitudinal changes in proteinuria and the risk of kidney failure remained consistent in the subgroup analysis limited to patients with IC-MPGN (Supplementary Table S3).

Proteinuria Reduction and Kidney Failure Risk

A second model analyzed the association between a ≥50% proteinuria reduction with the risk of kidney failure by dichotomizing proteinuria reduction at the 50% threshold (Table 3). The results showed that ≥ 50% proteinuria reduction during the follow-up time was significantly associated with a lower risk of kidney failure, in a model adjusted by the same covariables

Table 2. Joint model showing the association between the longitudinal change in proteinuria and the hazard of kidney failure

Model	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	2.50	2.19–2.88	<0.001
Time, mo	0.54	0.42–0.69	<0.001
Cox regression submodel			
Age			0.17
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	0.31	0.06–1.63	
Gender			0.52
Female	1.00 (reference)	1.00 (reference)	
Male	0.76	0.31–1.75	
Baseline eGFR			<0.001
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.06	0.01–0.25	
Histologic subtype			0.47
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.32	0.09–1.17	
IC-MPGN	0.92	0.27–3.16	
Total activity score			0.62
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	1.22	0.54–2.58	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	8.96	3.94–20.4	
Joint model			
Longitudinal change in proteinuria (per g/d increment)	3.18	1.95–5.83	<0.001

eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

Table 3. Joint model showing the association between a 50% reduction in proteinuria during follow-up time, and the hazard of kidney failure

Model	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	0.21	0.14–0.30	<0.001
Time, mo	1.08	1.06–1.09	<0.001
Cox regression submodel			
Age			0.97
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.04	0.35–3.37	
Gender			0.71
Female	1.00 (reference)	1.00 (reference)	
Male	1.15	0.56–2.35	
Baseline eGFR			<0.001
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.12	0.04–0.34	
Histologic subtype			0.37
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.39	0.14–1.13	
IC-MPGN	0.83	0.31–2.21	
Total activity score			0.85
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	0.92	0.43–1.91	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	7.51	3.24–13.4	
Joint model			
≥ 50% proteinuria reduction	0.61	0.46–0.75	<0.001

eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

(HR: 0.61; 95% CI: 0.46–0.75, $P < 0.001$). These results were further confirmed in subgroup analyses, focusing on patients with IC-MPGN (Supplementary Table S4), and a subset comparable to participants in ongoing trials with novel anticomplement agents[12,22,23] which included the following: individuals aged ≥ 12 years at baseline, with an eGFR ≥ 30 ml/min per 1.73 m^2 and baseline proteinuria ≥ 1 g/d ($n = 90$) (Supplementary Tables S5 and S6).

Furthermore, we investigated whether a smaller percentage reduction in proteinuria occurring earlier in the follow-up period could predict long-term kidney outcomes. Log-transformed HRs, adjusted for the same covariables were plotted against the percentage change in proteinuria at 6 and 12 months. The resulting graphs revealed a nonlinear trend between the percentage change in proteinuria and the risk of kidney failure, with reference values of −30% at 6 months, and −50% at 12 months (Figure 2c and d). Thus, we fitted censored versions of the previous joint model to evaluate the association between a 30% proteinuria reduction at 6 months and the risk of kidney failure and another model for the association between 50% proteinuria reduction at 12 months (Table 4). These analyses confirmed that ≥ 30% reduction at 6 months and ≥ 50% reduction at 12 months were associated with a lower risk of kidney failure. Specifically, the HRs were 0.91 (95% CI: 0.85–0.98, $P < 0.001$) at 6 months and 0.67 (95% CI: 0.61–0.78, $P < 0.001$) at 12 months. The results remained consistent in the subgroup analysis limited to patients with IC-MPGN (Table 5), irrespective of the overall follow-up (Supplementary Figure S6).

Proteinuria Reduction and eGFR Slope

Patients who achieved ≥ 30% proteinuria reduction at 6 months, or ≥ 50% reduction at 12 months had a significantly slower eGFR slope over time (Figures 3a and b). These results were confirmed by subgroup analyses of patients with IC-MPGN (Supplementary Figures S4 and S5). Moreover, kidney survival was significantly better in patients who achieved a percentage proteinuria reduction (Figure 3c and d).

TA-P and Kidney Outcomes

The long-term prognostic impact of persistent proteinuria on kidney outcomes over time was further evaluated by stratifying patients into 4 groups according to TA-P values: < 0.5 ($n = 23$), 0.5–1 ($n = 29$),

Table 4. Joint models for the association between a 30% proteinuria reduction at 6 months, and 50% proteinuria reduction at 12 months, and the hazard of kidney failure

Model A: 30% proteinuria reduction at 6 mo	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	0.24	0.13–0.46	<0.001
Time, mo	1.52	1.38–1.73	<0.001
Cox regression submodel			
Age			0.73
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.39	0.47–6.90	
Gender			0.28
Female	1.00 (reference)	1.00 (reference)	
Male	1.40	0.79–2.51	
Baseline eGFR			0.002
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.26	0.12–0.71	
Histologic subtype			0.31
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.46	0.23–1.02	
IC-MPGN	0.79	0.37–1.78	
Total activity score			0.65
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	0.86	0.41–1.68	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	8.95	4.68–22.4	
Joint model	0.91	0.85–0.98	<0.001
Model B: 50% proteinuria reduction at 12 mo	**Hazard ratio**	**95% confidence interval**	**P-value**
Linear mixed submodel			
Intercept	0.14	0.08–0.23	<0.001
Time, mo	1.22	1.16–1.28	<0.001
Cox regression submodel			
Age			0.85
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.14	0.37–4.11	
Gender			0.56
Female	1.00 (reference)	1.00 (reference)	
Male	1.26	0.62–2.91	
Baseline eGFR			<0.001
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.14	0.05–0.37	
Histologic subtype			0.37
Dense deposit disease	1.00 (reference)	1.00 (reference)	
C3 glomerulonephritis	0.36	0.11–1.19	
IC-MPGN	0.80	0.30–2.54	
Total activity score			0.90
< 9	1.00 (reference)	1.00 (reference)	
≥ 9	0.94	0.41–2.15	
Total chronicity score			<0.001
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	7.73	3.35–17.2	
Joint model	0.67	0.61–0.78	<0.001

eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex–mediated membranoproliferative glomerulonephritis.

1–3 ($n = 56$) and ≥ 3 g/d ($n = 41$) (Supplementary Table S7). Patients with TA-P ≥ 1 g/d were more likely to experience earlier progression to kidney failure than those with TA-P < 1 g/d (Figure 4). These results remained consistent when IC-MPGN cases were analyzed specifically (Supplementary Figure S7).

Table 5. Joint models for the association between a 30% proteinuria reduction at 6 months, and 50% proteinuria reduction at 12 months, and the hazard of kidney failure, only in patients with IC-MPGN

Model A: 30% proteinuria reduction at 6 mo	Hazard ratio	95% confidence interval	*P*-value
Linear mixed submodel			
Intercept	0.29	0.11–0.64	0.007
Time, mo	1.42	1.26–1.66	<0.001
Cox regression submodel			
Age			0.98
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.00	0.97–1.04	
Gender			0.72
Female	1.00 (reference)	1.00 (reference)	
Male	1.28	0.36–5.68	
Baseline eGFR			0.006
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.26	0.12–0.71	
Total chronicity score			0.006
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	1.27	1.03–1.59	
Joint model	0.72	0.58–0.90	<0.001
Model B: 50% proteinuria reduction at 12 mo	**Hazard ratio**	**95% confidence interval**	***P*-value**
Linear mixed submodel			
Intercept	0.14	0.08–0.23	<0.001
Time, mo	1.22	1.16–1.28	<0.001
Cox regression submodel			
Age			0.24
Pediatric	1.00 (reference)	1.00 (reference)	
Adult	1.02	0.98–1.08	
Gender			0.84
Female	1.00 (reference)	1.00 (reference)	
Male	1.21	0.32–6.27	
Baseline eGFR			0.14
< 60	1.00 (reference)	1.00 (reference)	
≥ 60	0.09	0.0–1.82	
Total chronicity score			0.01
< 4	1.00 (reference)	1.00 (reference)	
≥ 4	1.44	1.09–1.92	
Joint model	0.36	0.20–0.79	<0.001

eGFR, estimated glomerular filtration rate.

DISCUSSION

In this study, we conducted a comprehensive analysis of the relationship between proteinuria and kidney outcomes in a large multicenter cohort of patients with C3G and IC-MPGN. This study yields several key findings. First, we observed comparable kidney survival rates between patients with C3G and those with IC-MPGN. Second, we identified a significant association between longitudinal changes in proteinuria and the risk of progression to kidney failure, irrespective of the histological subtype. Third, we observed that

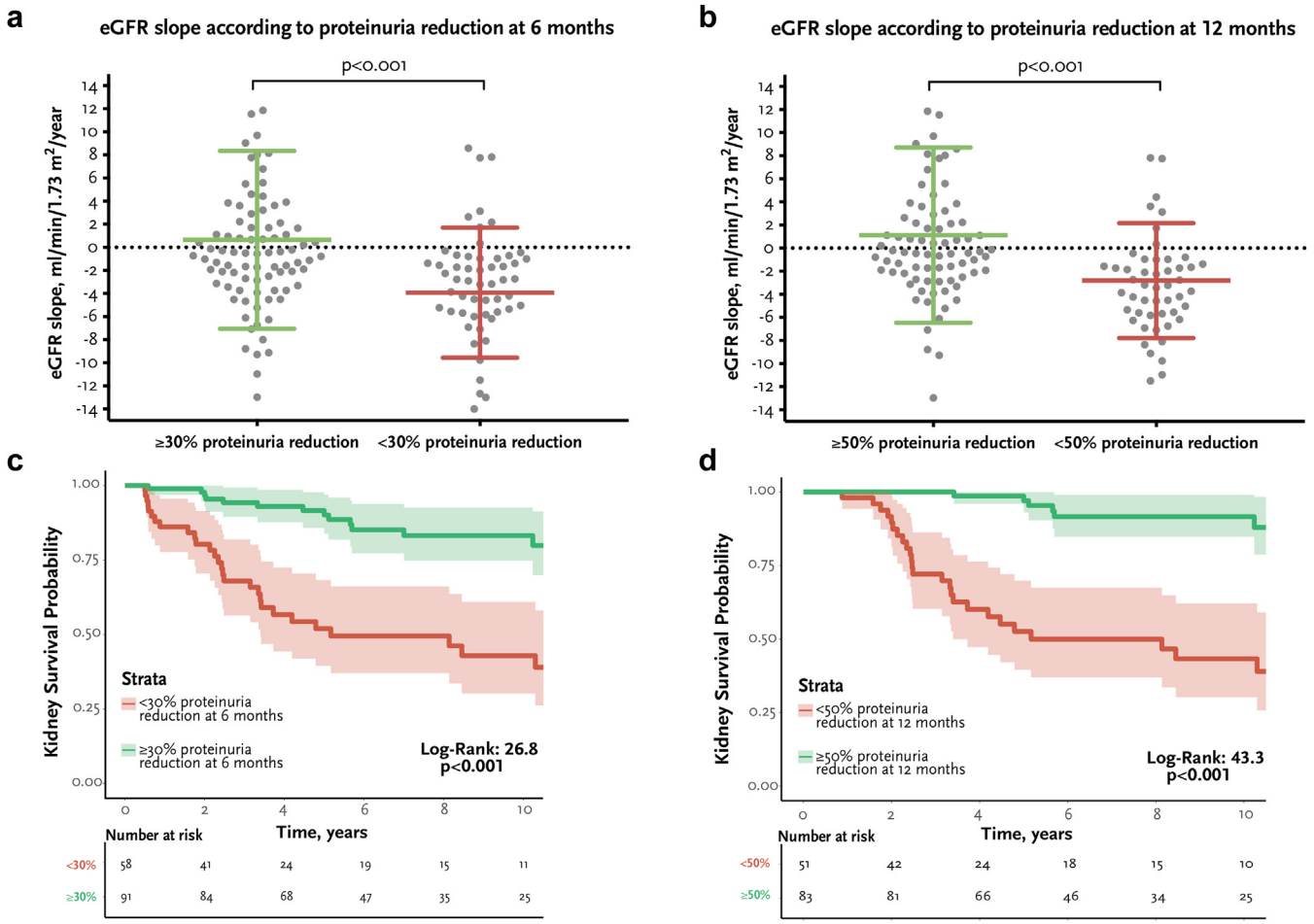

Figure 3. (a) eGFR slope according to proteinuria reduction at 6 months (≥ 30% vs. < 30%), (b) eGFR slope according to proteinuria reduction at 12 months (≥ 50% vs. < 50%), (c) Kaplan-Meier curves for kidney survival according to ≥ 30% proteinuria reduction at 6 months, (d) Kaplan-Meier curves for kidney survival according to ≥50% proteinuria reduction at 12 months. eGFR, estimated glomerular filtration rate.

≥ 50% proteinuria reduction was consistently associated with improved kidney outcomes in both C3G and IC-MPGN. Notably, these favorable outcomes were evident as early as 6 months following ≥ 30% reduction in proteinuria, or within 12 months when ≥ 50% reduction was achieved. Patients who achieved ≥ 30% proteinuria reduction at 6 months, or ≥ 50% reduction at 12 months exhibited a significantly slower eGFR slope over time. Finally, TA-P values > 1 g/d were significantly associated with poorer kidney survival, suggesting that achieving and maintaining proteinuria levels < 1 g/d should be the primary therapeutic goal in managing these conditions.

In recent years, several studies have evaluated the relationship between proteinuria and kidney outcomes in both C3G and IC-MPGN, although some findings have been inconsistent across cohorts.[19,24,25] Although some studies have identified baseline proteinuria as a prognostic marker for kidney failure, and efforts have been made to classify patients based on clinical profiles by considering both initial presentation and disease progression trajectory,[26] few studies have specifically investigated how longitudinal changes in proteinuria over time impact the risk of kidney failure. Our group previously found a strong association between longitudinal changes in proteinuria and the risk of kidney failure in a cohort of 85 patients exclusively with C3G.[17] In addition, we found that ≥ 50% proteinuria reduction during the follow-up time was significantly associated with a lower risk of kidney failure (HR: 0.79; 95% CI: 0.56–0.97; $P < 0.001$).[17] Conversely, another retrospective cohort study led by the Imperial College group, which included 75 patients with C3G or IC-MPGN with at least 2 years of follow-up, found no significant difference in outcome-free survival between those who achieved a 50% reduction in proteinuria and those who did not.[13] However, this study did observe that a doubling in proteinuria levels was associated with a 1.98-fold increased risk of reaching the outcome event. In contrast, analysis of 135 patients with C3G from the United Kingdom Rare Kidney Disease Registry showed that proteinuria at the time of diagnosis was a poor predictor of kidney failure risk, and that a reduction to levels below 100 mg/mmol

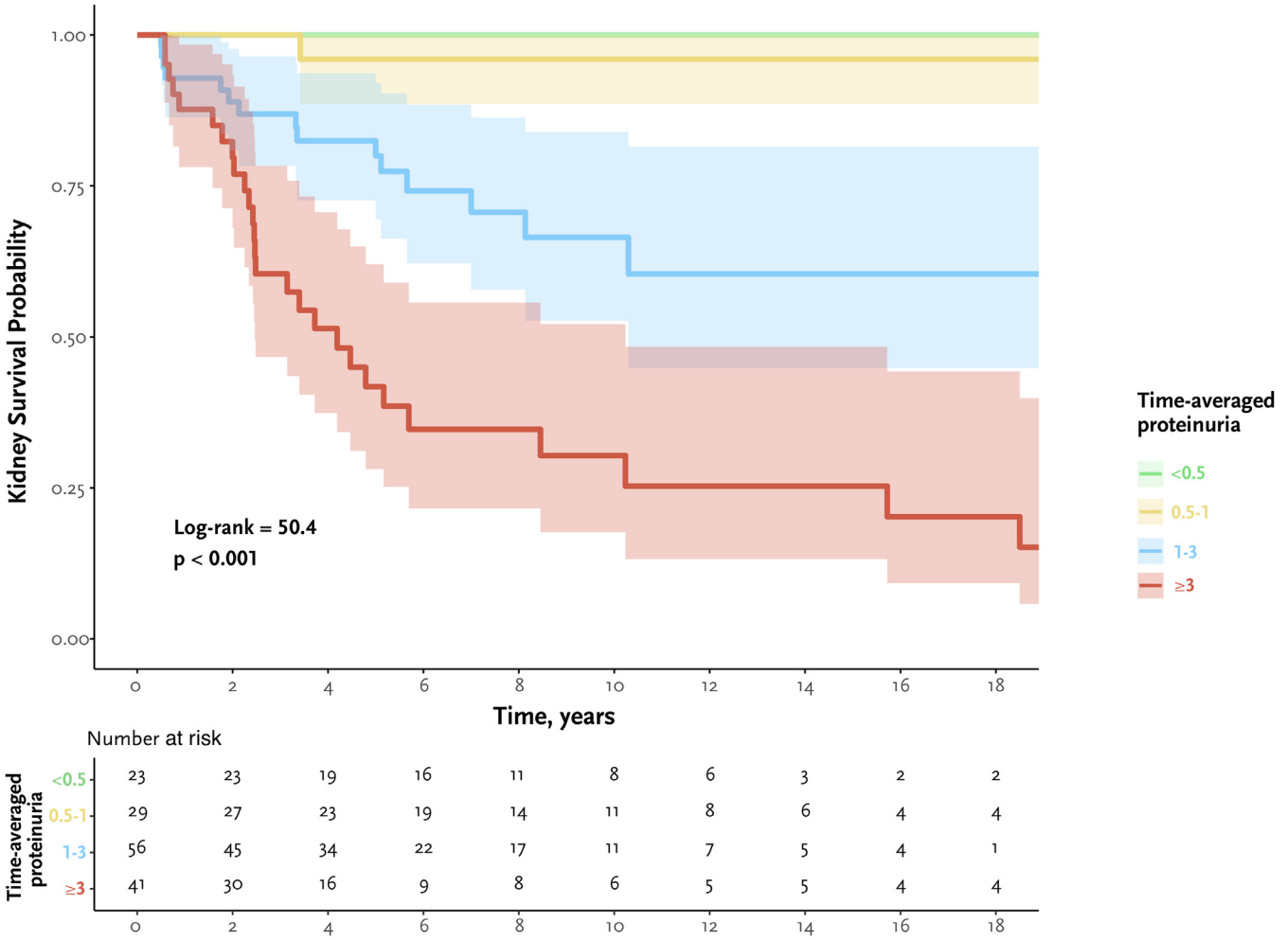

Figure 4. Kaplan-Meier curves for kidney survival according to time-averaged proteinuria over follow-up. Kidney survival was significantly worse for patients with persistent time-averaged proteinuria > 1 g/d.

creatinine/d (0.88 g/g) at 12 months, was associated with markedly reduced risk of kidney failure over 20 years (HR: 0.12; 95% CI: 0.02–0.62).[27]

Our study is one of the largest to date that incorporates longitudinal data from patients with both C3G and IC-MPGN. After rigorously excluding secondary forms of MPGN, for example, monoclonal gammopathies, currently recognized as a distinct subtype,[28] we successfully identified and included 51 cases of primary IC-MPGN, the majority of which were adults, for comparison with C3G. The baseline characteristics were properly balanced across histological subgroups, except for a higher proportion of pediatric patients with DDD. Consistent with previous studies,[14,16,27] we found no significant differences in kidney survival among patients with C3GN, DDD, or IC-MPGN, further supporting the notion that IC-MPGN may represent a distinct phenotype within the same C3G disease spectrum.[8,10,11]

Given the heterogeneity of C3G and IC-MPGN, there is a critical need to rely on early surrogate markers to assess treatment efficacy and guide clinical decisions. Strong evidence supports the biological link between proteinuria and progression to kidney failure across various kidney diseases, especially those marked by significant proteinuria.[29-31] Multiple factors could influence proteinuria levels within our cohort, including the degree of histologic activity, chronicity, baseline kidney function, and variations in treatment regimens. Our findings not only confirm the association between longitudinal changes in proteinuria and kidney outcomes in a large C3G cohort but also extend this association to patients with IC-MPGN. Notably, we identified 2 key target thresholds: ≥ 30% reduction in proteinuria within 6 months and ≥ 50% reduction within 12 months, both of which were independently associated with improved kidney outcomes. The patients who achieved these reductions also experienced a slower decline in eGFR over time. Thus, although proteinuria has certain limitations as a surrogate marker,[32] our results strongly support its use as a valuable end point in clinical trials of new therapies

targeting both C3G and IC-MPGN. Supporting this perspective, results from phase 2 and preliminary phase 3 clinical trials of novel proximal complement inhibitors, such as pegcetacoplan and iptacopan, have demonstrated a significant reduction in proteinuria following treatment.[33–38]

Another remarkable finding of our study was the identification of potential long-term target proteinuria levels in patients with C3G or IC-MPGN. Consistent with other glomerular diseases, such as IgA nephropathy,[39,40] we showed that patients with TA-P $<$ 1 g/d had significantly improved kidney survival. From a clinical perspective, this underscores the critical importance of not only achieving short-term reductions in proteinuria but also sustaining an optimal target of $<$ 1 g/d during follow-up to effectively slow disease progression in C3G or IC-MPGN.

This study has important limitations. First, given the retrospective nature of this study, no causal relationships were established. Second, the underrepresentation of pediatric patients with IC-MPGN, likely because of the lower participation of pediatric nephrologists in data collection or a lower incidence in the pediatric population, led to demographic imbalances between the C3G and IC-MPGN groups. Subgroup and propensity score matching analyses were performed to overcome this limitation. Third, the heterogeneity in the initial clinical presentation and the wide range of therapeutic strategies used at the discretion of the treating physicians may have introduced variability in eGFR values and influenced the trend of proteinuria at certain time points. Lastly, although we adjusted for baseline and histological characteristics using joint modeling, residual confounding factors related to unmeasured variables or differences in patient management over time may still exist. Despite these limitations, this study enhanced our understanding of the natural history of the disease and provided compelling evidence supporting the role of proteinuria as a valuable surrogate marker of kidney outcomes in patients with both C3G and IC-MPGN.

In conclusion, by leveraging longitudinal data from a large multicentric cohort of patients with C3G and IC-MPGN, our results show that a reduction in proteinuria, specifically, $\geq$ 30% reduction within 6 months and $\geq$ 50% reduction within 12 months– is associated with significantly improved kidney outcomes and a slower decline in eGFR. These findings underscore the potential utility of proteinuria as an early end point in clinical trials and offer a practical and meaningful measure for evaluating the efficacy of new therapies targeting C3G and IC-MPGN. Further prospective studies are required to clarify and deepen our understanding of this association.

APPENDIX

List of the Spanish Group for the Study of Glomerular Diseases

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DISCLOSURE

FC-F reports fees from Novartis, Apellis, SOBI, and AstraZeneca outside the submitted work. JL-PC reports fees from CSL Vifor, Novo Nordisk, and AstraZeneca outside the submitted work. AH reports personal fees from GSK, AstraZeneca, and Alexion outside the submitted work. GFJ reports fees from GSK, Otsuka, AstraZeneca, and Novartis outside the submitted work. MP reports fees from Alexion, Apellis, Vifor, GSK, Novartis, Otsuka, STADA, and Travere and loyalties from UpToDate. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Research idea and study design was done by FC-F, and MP. Data acquisition was done by all the authors. Statistical analysis was done by FC-F and MP. Supervision or mentoring was done by MP. Each author contributed important intellectual content during manuscript drafting or revision, agreed to be personally accountable for the individual's own contributions, and ensured that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, were appropriately investigated and resolved, including documentation in the literature, if appropriate.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. Supplementary information on the C3G histological index.

Figure S1. Flowchart of the study population.

Figure S2. Distribution of propensity scores and standardized differences before and after matching.

Figure S3. Kaplan-Meier curves for kidney survival according to histologic subtypes in the propensity score-matched subcohort.

Figure S4. Kaplan-Meier curves for kidney survival according to $\geq$ 30% proteinuria reduction at 6 months, in patients with IC-MPGN.

Figure S5. Kaplan-Meier curves for kidney survival according to $\geq$ 50% proteinuria reduction at 12 months, in patients with IC-MPGN.

Figure S6. Kaplan-Meier curves for kidney survival according to $\geq$ 30% proteinuria reduction at 6 months, or $\geq$ 50% proteinuria reduction at 12 months, by follow-up $<$ 60 months, or $\geq$ 60 months.

Figure S7. Kaplan-Meier curves for kidney survival according to time-averaged proteinuria values in patients with IC-MPGN.

Table S1. Additional patient characteristics according to histological subtype.

Table S2. Baseline demographic and clinical characteristics according to histological subtype in the propensity score-matched sub cohort.

Table S3. Joint model showing the association between longitudinal changes in proteinuria and risk of kidney failure in patients with IC-MPGN.

Table S4. Joint model showing the association between a 50% reduction in proteinuria during the follow-up period and the risk of kidney failure in patients with IC-MPGN.

Table S5. Baseline clinical characteristics of patients aged $\geq$ 12 years at baseline, with an eGFR $\geq$ 30 ml/min per 1.73 m^2 and baseline proteinuria $\geq$ 1 g/d.

Table S6. Joint model showing the association between a f50% reduction in proteinuria during the follow-up time and the risk of kidney failure in patients similar to those enrolled in clinical trials.

Table S7. Clinical characteristics of patients according to time-averaged proteinuria values.

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