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Development and validation of a nomogram to predict kidney survival at baseline in patients with C3 glomerulopathy

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ABSTRACT

Background. C3 glomerulopathy is a rare and heterogeneous complement-driven disease. It is often challenging to accurately predict in clinical practice the individual kidney prognosis at baseline. We herein sought to develop and validate a prognostic nomogram to predict long-term kidney survival.

Methods. We conducted a retrospective, multicenter observational cohort study in 35 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases. The dataset was randomly divided into a training group ($n = 87$) and a validation group ($n = 28$). The least absolute shrinkage and selection operator (LASSO) regression was used to screen the main predictors of kidney outcome and to build the nomogram. The accuracy of the nomogram was assessed by discrimination and risk calibration in the training and validation sets.

Results. The study group comprised 115 patients, of whom 46 (40%) reached kidney failure in a median follow-up of 49 months (range 24–112). No significant differences were observed in baseline estimated glomerular filtration rate (eGFR), proteinuria or total chronicity score of kidney biopsies, between patients in the training versus those in the validation set. The selected variables by LASSO were eGFR, proteinuria and total chronicity score. Based on a Cox model, a nomogram was developed for the prediction of kidney survival at 1, 2, 5 and 10 years from diagnosis. The C-index of the nomogram was 0.860 (95% confidence interval 0.834–0.887) and calibration plots showed optimal agreement between predicted and observed outcomes.

Conclusions. We constructed and validated a practical nomogram with good discrimination and calibration to predict the risk of kidney failure in C3 glomerulopathy patients at 1, 2, 5 and 10 years.

GRAPHICAL ABSTRACT
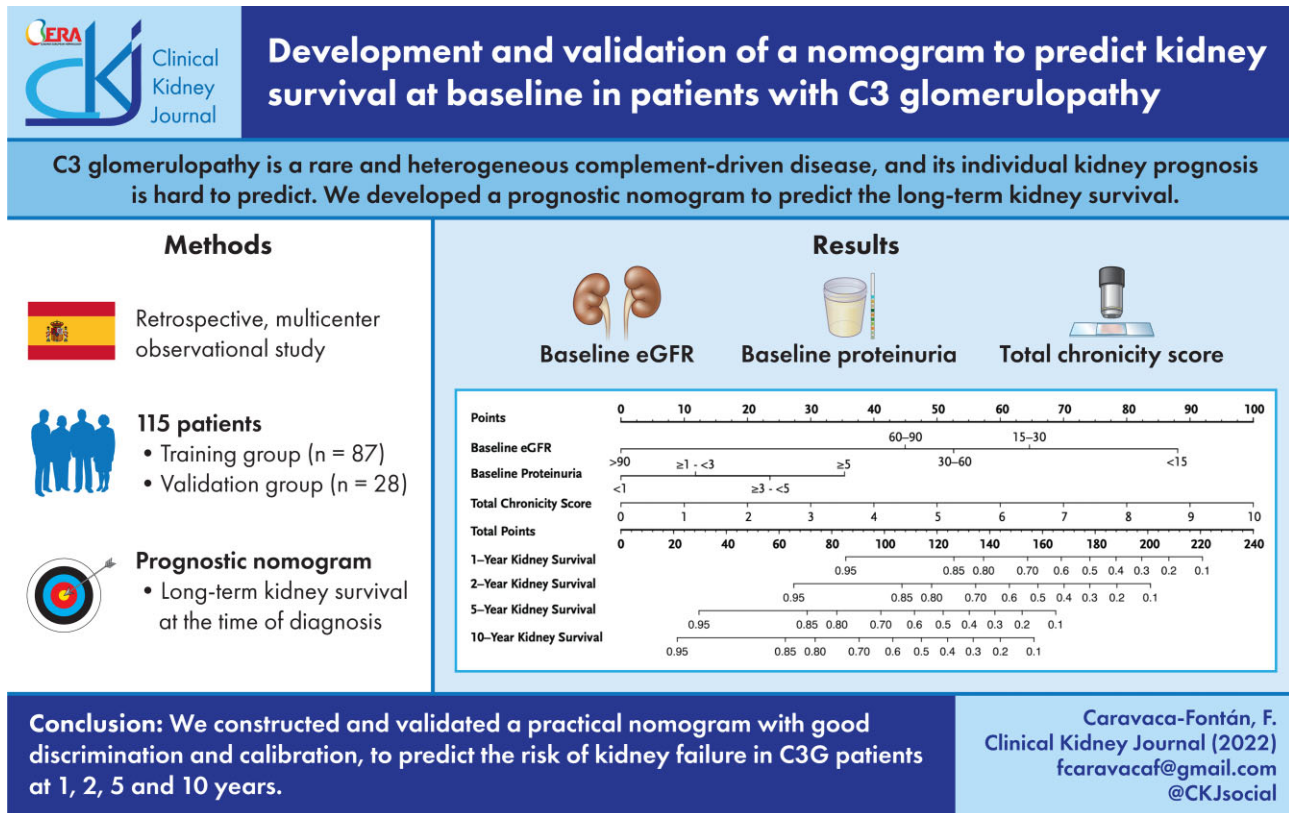
Keywords: C3 glomerulopathy, calibration, discrimination, kidney failure, nomogram

INTRODUCTION

C3 glomerulopathy (C3G) represents a heterogeneous group of glomerular diseases characterized by an overactivation of the alternative complement pathway in plasma and glomerular microenvironment, resulting in the deposition of the C3 molecule and its degradation fragments that are detectable in a kidney biopsy [1, 2].

In recent years, several important efforts have led to a better understanding of the pathogenesis and natural history of C3G [1, 3]. However, the often slowly progressive and pauci-symptomatic course of the disease at its early stages may lead to a delayed diagnosis of the disease in many cases, with the consequent development of irreversible chronic histologic lesions [3, 4]. In fact, the extent of disease chronicity in kidney biopsy has been recognized as a major predictor of kidney outcomes in C3G [4, 5].

The results from the largest cohort studies on C3G have revealed that among the most important predictors of kidney survival are the age at diagnosis, the estimated glomerular filtration rate (eGFR) and the degree of proteinuria at the time of clinical presentation, together with the disease chronicity on kidney biopsy [5–10]. In addition, our group recently found a strong association between the longitudinal change in proteinuria and the risk of kidney failure, which could provide clinicians a dynamic prediction of kidney outcomes during follow-up [11]. However, considering the high heterogeneity of C3G patients, it

is often challenging to accurately predict in clinical practice the individual kidney prognosis at baseline. Thus the development of a nomogram (i.e. a multivariable visualization prediction tool) could provide clinicians an intuitive tool for prediction of kidney outcomes at baseline, and this information could also be relevant for research purposes in C3G.

Nomograms have been widely used in oncology to predict outcomes of patients with malignant tumors [12]. However, to the best of our knowledge, no study has proposed a nomogram to predict the prognosis of C3G patients based on the clinical and histologic features at the time of diagnosis.

Hence, in this study, we aimed to construct and validate a prognostic nomogram to predict the long-term kidney survival at the time of diagnosis in a multicentric cohort of patients with C3G.

MATERIALS AND METHODS

Study patients

Patients diagnosed with C3 glomerulopathy between January 1995 and June 2020 in 35 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases (GLOSEN) were enrolled. Patients with other underlying autoimmune diseases, infected with hepatitis B or C or those with missing data were excluded.

The diagnosis of C3G was based on the 2013 Consensus Guidelines criteria, which required C3 staining on immunofluorescence at least two orders of magnitude greater than any immunoglobulin staining [13]. Patients were considered to have dense deposit disease (DDD) when highly electron-dense intramembranous deposits were observed on electron microscopy, and C3 glomerulonephritis (C3GN) when deposits did not fulfill this criterion. Baseline and follow-up data were compiled from the medical records of all participating centers, as described elsewhere [4, 7].

Kidney biopsy specimens were examined in the pathology departments of the participating hospitals. The degree of disease activity and chronicity was analyzed according to the previously published C3G histologic index [4, 5], using a semiquantitative scale of 0–3, except for arteriosclerosis, which was scored as 0–1. Total activity and chronicity scores were then calculated as the sum of each individual item, with a total possible score of 21 for activity lesions and a total possible score of 10 for chronic lesions.

All patients gave written informed consent. The study was approved by the institutional review board of Hospital Universitario 12 de Octubre and was conducted in accordance with the Declaration of Helsinki.

Definitions and outcome

Baseline was defined as the time at which the kidney biopsy was performed and follow-up period as the interval of time elapsed between the kidney biopsy and the last outpatient visit or kidney failure.

Nephrotic syndrome was defined as a proteinuria of >3.5 g/day along with serum albumin <3 g/dL. Nephritic syndrome was defined as the combination of hematuria, nonnephrotic proteinuria, hypertension and kidney function impairment. Asymptomatic urinary abnormalities were defined by the presence of nonnephrotic proteinuria and/or persistent microscopic hematuria >5 erythrocytes per high power field.

The main outcome was kidney failure, defined as an eGFR <15 mL/min/1.73 m^2, the need for dialysis or preemptive kidney transplantation.

Statistical analyses

We conducted a retrospective, multicenter observational cohort study. Descriptive statistics are presented as mean ± standard deviation or median and interquartile range (IQR) for continuous variables and absolute values and percentages for categorical variables. Parametric and nonparametric tests were chosen as appropriate for descriptive comparisons of continuous variables and the chi-squared test for categorical variables. For the comparisons in smaller groups we performed a Fisher's exact test.

The dataset was randomly divided into a training group ($n =$ 87) and a validation group ($n =$ 28), with a ratio of 3:1. The training group was used for the development and internal validation of the nomogram whereas the validation group was used to verify the model.

The least absolute shrinkage and selection operator (LASSO) regression was used to screen the main predictors of kidney outcome in order to avoid collinearity of covariates. The predictors selected by LASSO regression were incorporated into a Cox proportional hazards regression model to build the nomogram, following the methodology described elsewhere [12, 14, 15]. Kidney survival at 1, 2, 5 and 10 years was estimated.

The accuracy of the nomogram was assessed by discrimination [using C-index and time-dependent receiver operating characteristics (ROC) curves, with the corresponding area under the curve (AUC)] and risk calibration, in the training and validation groups. To further analyze the discrimination of the nomogram, a total score was calculated for each patient and then stratified into two groups based on the median scores. Distributions of time to kidney failure were depicted by survival curves using the Kaplan–Meier method and the survival curves were compared using the logrank test.

A P-value <.05 was considered to be significant. Analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and the R packages 'caret', 'glmnet', 'rms', 'nomogramEx', 'survival', 'ggplot2', 'Hmisc', 'survival', 'survivalROC' and 'survminer'.

RESULTS

Baseline characteristics

The study group comprised 115 patients with a median age of 30 years (IQR 19–50), 44% of whom were female (Table 1). The median baseline eGFR was 54 mL/min/1.73 m^2 (IQR 23–106) and the median baseline proteinuria was 3 g/day (IQR 1.6–5.7). An inverse correlation was observed between eGFR and proteinuria, as well as eGFR and total chronicity score (Supplementary data, Figure S1).

Eighteen patients (16%) received nonimmunosuppressive therapies, whereas 15 patients received corticosteroids alone (13%), 46 corticosteroids plus mycophenolate mofetil (40%), 7 rituximab (6%), 10 eculizumab (9%) and 19 received other immunosuppressive regimens (Supplementary data, Tables S1 and S2).

Overall, 46 patients (40%) reached kidney failure in a median follow-up of 49 months (IQR 24–112). The kidney survival rate was 80% at 1 year, 75% at 2 years, 61% at 5 years and 24% at 10 years. No significant changes were observed in the kidney outcomes of patients according to the year of diagnosis (Supplementary data, Figure S2).

After randomly splitting the sample, 87 patients were assigned to the training group and 28 to the validation group. The median eGFR and proteinuria in the training group were 53 mL/min/1.73 m^2 (IQR 20–106) and 3 g/day (IQR 1.6–5.7), respectively. In contrast, the median eGFR and proteinuria in the validation group were 55 mL/min/1.73 m^2 (IQR 27–110) and 3.1 g/day (IQR 2–6.6), respectively. No significant differences were observed in baseline eGFR, proteinuria or total chronicity scores between patients in the training versus those in the validation group (Table 1). Thirty-five (40%) patients in the training group reached kidney failure versus 11 (39%) in the validation group.

Development of the nomogram

A total of 10 variables were included in the LASSO model: age, gender, presence of complement pathogenic variants and antibodies against complement components, baseline eGFR, serum albumin, serum C3 levels, proteinuria, total activity and chronicity scores, of which 3 variables were left with nonzero coefficients. The selected variables included baseline eGFR, proteinuria and total chronicity score. The respective coefficients of these factors were calculated when log lambda was 2.36 (Fig. 1A and B). The three variables obtained by LASSO regression were included in the Cox proportional hazards regression model (Table 2), and emerged as independent predictors of kidney failure. Based on the Cox model, a nomogram was developed for the prediction of kidney survival at 1, 2, 5 and 10 years (Fig. 2).

Table 1. Clinical characteristics of study patients

Characteristics	Total (n = 115)	Training cohort (n = 87)	Validation cohort (n = 28)	P-value
Baseline				
Age (years), median (IQR)	30 (19–50)	30 (19–48)	30 (15–54)	.91
Sex, female (%)	51 (44)	41 (47)	10 (36)	.29
Hypertension, n (%)	75 (65)	56 (64)	19 (68)	.74
Antecedent infection, n (%)	29 (25)	21 (24)	8 (29)	.64
C3GN/DDD, n (%)	95 (83) / 20 (17)	73 (84)/14 (16)	22 (79)/6 (21)	.52
Clinical presentation, n (%)				.75
Nephrotic syndrome	46 (40)	36 (42)	11 (39)	
Nephritic syndrome	34 (30)	26 (30)	8 (29)	
Isolated nonnephrotic proteinuria	15 (13)	9 (10)	5 (18)	
Asymptomatic urinary abnormalities	20 (17)	16 (18)	4 (14)	
Creatinine at diagnosis (mg/dL), median (IQR)	1.4 (0.8–3)	1.4 (0.8–3)	1.5 (0.8–2.2)	.73
eGFR (mL/min/1.73 m^2), median (IQR)				.81
>90	37 (32)	29 (33)	8 (29)	
60–90	11 (10)	8 (9)	3 (11)	
30–60	26 (23)	18 (21)	8 (29)	
15–30	19 (16)	13 (15)	6 (21)	
<15	22 (19)	19 (22)	3 (11)	
Serum albumin (g/dL), median (IQR)	3.1 (2.5–3.8)	3.1 (2.5–3.8)	3.1 (2.4–3.9)	.58
Serum C3 (mg/dL), median (IQR)	65 (27–90)	65 (35–90)	65 (20–98)	.75
Serum C4 (mg/dL), median (IQR)	24 (17–31)	25 (18–31)	22 (16–28)	.26
Proteinuria (g/24 h), n (%)				.93
<1	15 (13)	12 (14)	3 (11)	
≥1–<3	39 (34)	31 (35)	9 (32)	
≥3–<5	26 (23)	18 (21)	7 (25)	
≥5	35 (30)	26 (30)	9 (32)	
Follow-up (months), median (IQR)	49 (24–112)	46 (22–96)	52 (24–112)	.25
Alternative complement pathway studies[a], n (%)				
Complement pathogenic variants	23 (20)	15 (17)	8 (29)	.19
Variants of unknown significance	41 (36)	31 (36)	10 (36)	.99
Antibodies against complement components	33 (29)	24 (28)	9 (32)	.64
Kidney biopsy				
Immunofluorescence, n (%)				.21
C3 alone	54 (47)	38 (44)	16 (57)	
C3 dominant	61 (53)	49 (56)	12 (43)	
C3G histologic index—activity score, median (IQR)				
Mesangial hypercellularity (0–3)	3 (2–3)	3 (2–3)	3 (2–3)	.31
Endocapillary proliferation (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	.93
Membranoproliferative morphology (0–3)	3 (0–3)	3 (0–3)	3 (1–3)	.54
Leukocyte infiltration (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	.19
Crescent formation (0–3)	0 (0–1)	0 (0–1)	0 (0)	.26
Fibrinoid necrosis (0–3)	0 (0)	0 (0)	0 (0)	.72
Interstitial inflammation (0–3)	0 (0–1)	0 (0–1)	1 (0–1)	.90
Total activity score (0–21)	8 (6–10)	7 (6–10)	8 (5–11)	.52
C3G histologic index—chronicity score, median (IQR)				
Global/segmental glomerulosclerosis (0–3)	1 (0–2)	1 (0–2)	1 (0–1)	.61
Tubular atrophy (0–3)	1 (0–2)	1 (0–1)	1 (0–2)	.52
Interstitial fibrosis (0–3)	1 (0–2)	1 (0–2)	1 (0–2)	.41
Arterio- and arteriolosclerosis (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	.65
Total chronicity score (0–10)	3 (1–6)	3 (1–5)	3 (0–6)	.92

[a]A complete description of pathogenic variants and antibodies against complement components are described in Supplementary data, Tables S3 and S4.

According to the nomogram, each variable is assigned a score according to the category ('points') and the total score is computed by summing individual scores ('total points'). The corresponding kidney survival probability suggested by the nomogram at each time point (1, 2, 5 and 10 years) can be obtained from the total points obtained.

As an example of nomogram usage, a patient with an eGFR of 45 mL/min/1.73 m^2 with a proteinuria of 5.2 g/day at the time of clinical diagnosis and a total chronicity score of 6 would obtain a total score of 147.5 (52.5 + 35 + 60). Thus the corresponding kidney survival probability of this patient would be 74%, 60%, 25% and 17% at 1, 2, 5 and 10 years, respectively.
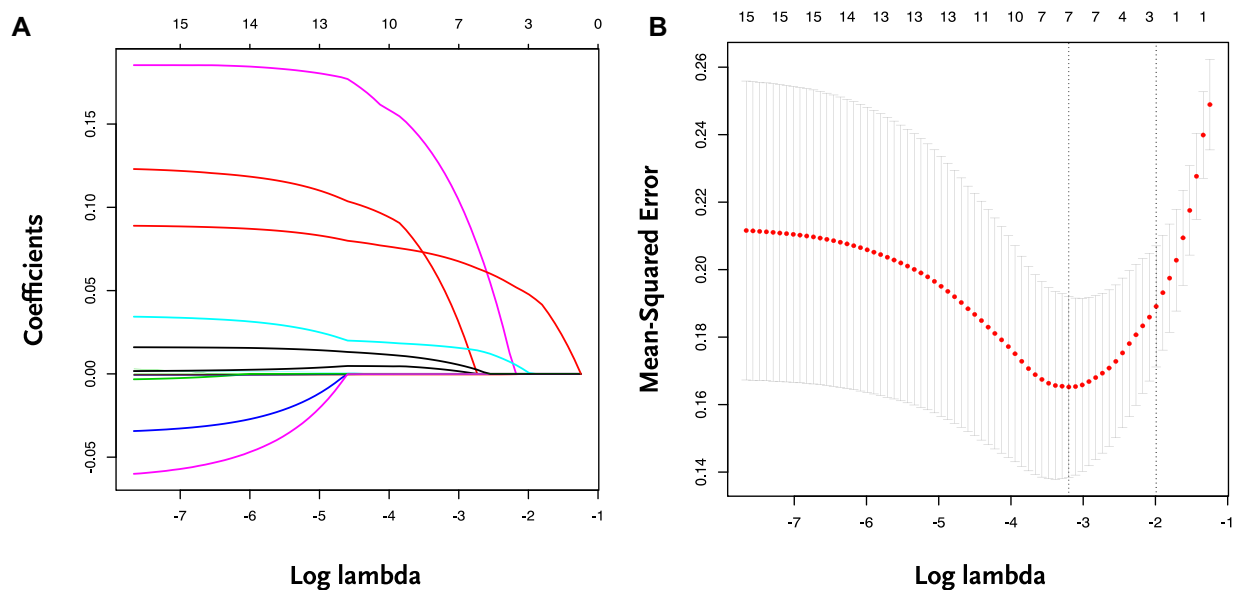
FIGURE 1: (**A**) LASSO coefficient profiles of the 10 variables included in the model against the log lambda. This analysis resulted in the selection of three factors: eGFR, proteinuria and total chronicity score. (**B**) Relationship between the log lambda and the mean-squared error in the LASSO regression. Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the one standard error of the minimum criteria.

Table 2. Multivariable Cox regression analysis

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	P-value
eGFR (mL/min/1.73 m^2)				.01
>90	1.00 (reference)	1.00 (reference)	1.00 (reference)	
60–90	2.11	0.69	9.19	
30–60	2.63	1.03	4.16	
15–30	3.47	1.62	5.53	
<15	6.78	2.49	9.98	
Proteinuria (g/day)				.002
<1	1.00 (reference)	1.00 (reference)	1.00 (reference)	
≥1–<3	2.12	1.17	5.84	
≥3–<5	2.11	1.22	5.78	
≥5	4.59	2.43	7.67	
Total chronicity score	1.36	1.19	1.56	<.001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

Internal validation

The validation of the model was based on discrimination and calibration. The C-index of the nomogram was 0.860 [95% confidence interval (CI) 0.834–0.887]. Figure 3A depicts time-dependent ROC curves of the training group. The AUCs were 0.87, 0.91, 0.90 and 0.91 at 1, 2, 5 and 10 years, respectively. Figure 3B depicts calibration plots at the same time points, showing an optimal agreement between predicted and observed outcomes.

The median total points obtained from the nomogram in the overall cohort was 98 (IQR 43–131). Based on these median values, the training group was divided into high risk and low risk, depending on whether the values were above or below the median. The median survival time in the high-risk and low-risk groups was 20 and 258 months, respectively. A Kaplan–Meier curve (Fig. 3C) illustrated that this model has good performance in identifying the population with different risk levels (P < .0001).

External validation

The C-index of the nomogram for the prediction of kidney survival in the validation set was 0.865 (95% CI 0.815–0.914). Figure 4A depicts time-dependent ROC curves of the validation group. The AUCs were 0.92, 0.92, 0.86 and 0.93 at 1, 2, 5 and 10 years, respectively. Likewise, the calibration plot depicted in Figure 4B showed overall optimal agreement between predicted and observed values. Finally, Kaplan–Meier curves according to median total points of the nomogram showed a significant difference in kidney survival between patients categorized as high risk and those categorized as low risk.

DISCUSSION

In this study we constructed and validated a nomogram for predicting kidney failure in patients with C3G based on a large multicentric cohort of patients with this disease. There are several major findings in this study. First, through LASSO
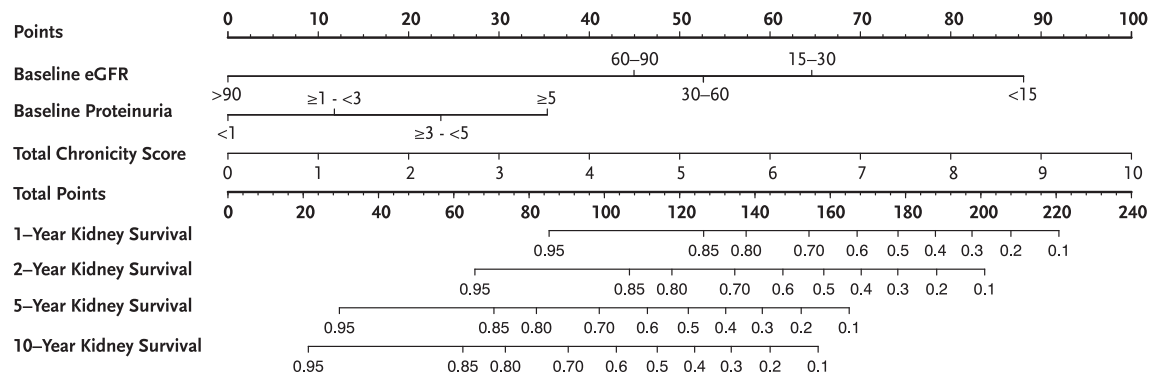
FIGURE 2: Nomogram for the prediction of kidney failure at 1, 2, 5 and 10 years. Locate the patient's variable and draw a line up to the 'points' axis to find the value for each variable. Calculate the total point value by summing the scores of each variable. Then locate the total point value on the 'total points' axis and draw a line down to the 1-year kidney survival axis, the 2-year kidney survival axis, the 5-year kidney survival axis or the 1-year kidney survival axis to obtain the likelihood of kidney failure at 1, 2, 5 and 10 years. Please note that eGFR was measured as mL/min/1.73 m^2 and proteinuria as g/day. Example: A patient with a baseline eGFR of 65 mL/min/1.73 m^2, proteinuria of 2 g/day and total chronicity score of 3 would obtain a total score of 87 (45 + 12 + 30). Thus the corresponding kidney survival probability for this patient would be 94%, 90%, 77% and 72% at 1, 2, 5 and 10 years, respectively.

regression we screened for the main risk factors of kidney failure, among which we found baseline eGFR, proteinuria and total chronicity score from Columbia University's C3G Histologic Index [5]. These variables were analyzed by Cox regression to calculate the kidney survival of patients and were finally used to construct the nomogram. Second, our results showed that this nomogram performs well in distinguishing between patients at high and low risk of developing kidney failure. Third, the kidney prognosis of C3G patients was also accurately predicted based on these parameters at diagnosis, suggesting that this model could be implemented in routine clinical practice.

Nomograms represent a visualization of a complex model equation in which the behavior of predictors is represented in scales [15]. Nomograms have become an attractive and useful clinical tool, as they provide estimates of the probability of an event, tailored to the profile of individual patients [12]. They provide clinicians with an estimate of prognosis that, in the case of C3G, is of great interest and can help in titrating the intensity of treatment at baseline.

In our study, the main predictors of kidney failure were eGFR, proteinuria and the total disease chronicity in the kidney biopsy. We used the LASSO method for variable selection to avoid overfitting of the model [16]. However, unlike in previous studies [4, 7], the use of the different treatment strategies was not included in the regression model since the main objective was to develop a predictive model at baseline in treatment-naïve patients.

Our results are in line with those reported in other case series. For instance, in the study by Servais *et al.* [10], baseline eGFR correlated well with eGFR at the last follow-up and kidney survival was found to be worse in patients with baseline eGFR <60 mL/min/1.73 m^2. In the study by Caliskan *et al.* [6], the main predictors of kidney failure were age at diagnosis, eGFR, proteinuria and percentage of crescentic/sclerotic glomeruli, together with the degree of interstitial fibrosis. Likewise, Ravindran *et al.* [8] found age at diagnosis, serum creatinine, proteinuria >3 g/day, glomerulosclerosis and degree of interstitial/tubular atrophy as the main predictors of kidney failure or doubling of serum creatinine. In contrast, in the study by Medjeral-Thomas *et al.* [9], kidney impairment at presentation only predicted worse outcomes in patients with DDD. In contrast, in the study by Bomback *et al.* [5], baseline eGFR emerged as the only clinical variable associated with kidney failure and, unlike ours, both

total disease activity and chronicity were significantly associated with the primary outcome.

In an attempt to identify patients at higher risk of kidney failure, in our study we further stratified patients into two groups based on the median score obtained from the predictive nomogram. Despite sample size constraints—particularly in the validation group—we managed to identify and confirm in the validation group a numerical threshold for the classification of patients as high or low risk.

Finally, we assessed the accuracy of the proposed nomogram through discrimination, which is the ability to accurately rank individuals' risk, and calibration, which represents the agreement between observed and predicted risks [17], and found overall good performance of the model.

Taken together, the results of this study combined with those reported in another subanalysis from our group [11] suggest that the nomogram would be an appropriate clinical tool be used in patients with C3G for the prediction of prognosis at baseline, whereas the longitudinal evaluation of proteinuria at each visit would be more suitable to dynamically predict outcomes. In contrast, although we only included C3G without underlying monoclonal gammopathy [18–20], the similarities in several clinical and pathologic features with C3G patients with monoclonal gammopathy could justify the use of this nomogram for the prediction of prognosis of these patients at baseline. However, further studies are warranted to validate this hypothesis.

Several limitations should be acknowledged. First, due to the observational and retrospective nature of the study, no causal relationships can be established. Second, only variables known to be determinants of prognosis were included in the model and thus we cannot rule out that other unmeasured confounders could have a prognostic influence. Third, although in this study we were able to identify C3G patients with poor short- and medium-term kidney prognosis, longer follow-up may be necessary to fully validate these results. Despite these limitations, this study collected a large series of patients with C3G that allowed us to construct a predictive nomogram and further contributes to the understanding of the natural history and prognosis of the disease.

In conclusion, in this study we found that eGFR, proteinuria and total chronicity score at baseline were the main predictors of
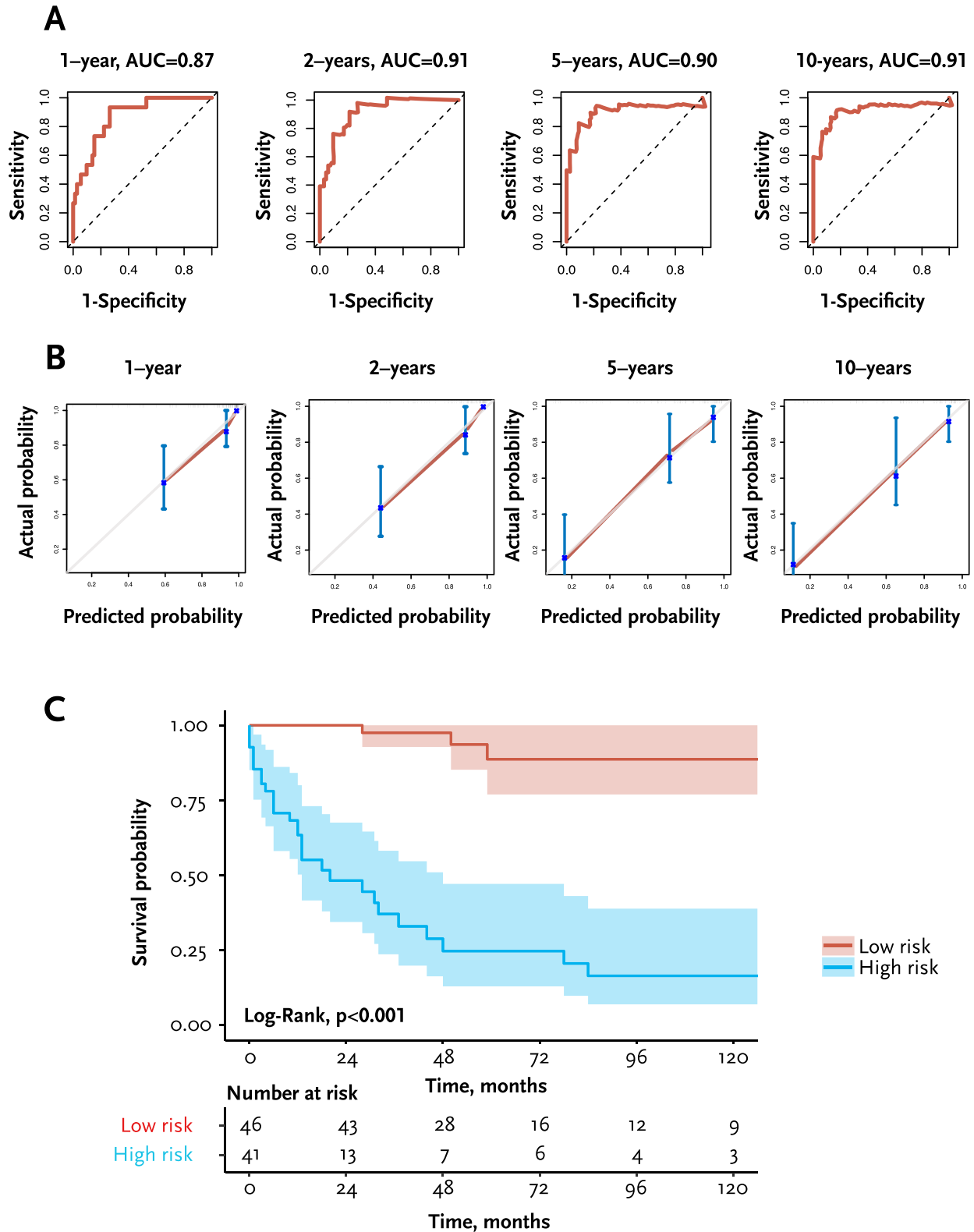
FIGURE 3: (**A**) ROC curves of the training group, with their corresponding AUC at the different time points (1, 2, 5 and 10 years). (**B**) Calibration curves of predicted versus actual probabilities of kidney failure at different time points (1, 2, 5 and 10 years). The gray line represents an ideal agreement between actual and predicted probabilities. The red line represents our nomogram and the vertical bars represent 95% CIs. (**C**) Kaplan–Meier curve for kidney survival in the high-risk versus low-risk group (based on the total score of the predictive nomogram at the threshold of 98 points).
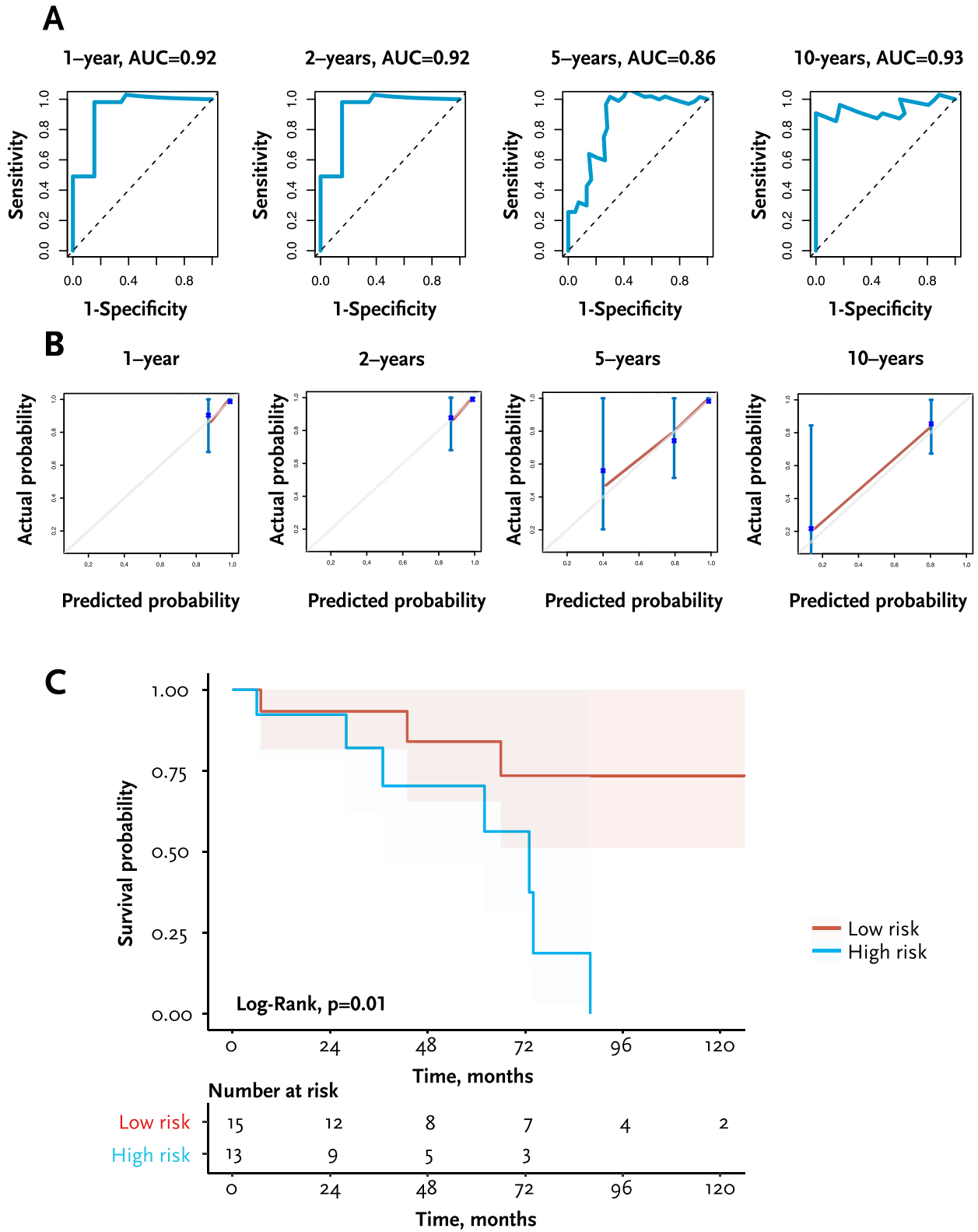
FIGURE 4: (**A**) ROC curves of the validation group, with their corresponding AUC at the different time points (1, 2, 5 and 10 years). (**B**) Calibration curves of predicted versus actual probabilities of kidney failure at different time points in the validation group (1, 2, 5 and 10 years). The gray line represents an ideal agreement between actual and predicted probabilities, the red line represents our nomogram and the vertical bars represent 95% CIs. (**C**) Kaplan–Meier curve for kidney survival in the high-risk versus low-risk group of the validation group.

kidney failure in C3G patients. Furthermore, a simple and easy-to-use nomogram with good discrimination and calibration was constructed and validated in this study to predict the risk of kidney failure in C3G patients at 1, 2, 5 and 10 years.

DATA AVAILABILITY STATEMENT

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

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

F.C.-F. reports personal fees from Novartis outside the submitted work. M.D.-E. reports personal fees from Novartis outside the submitted work. G.A. reports personal fees and nonfinancial support from Alexion Pharmaceuticals, personal fees and nonfinancial support from Recordati Rare Diseases, Advincenne and Kyowa Kirim and personal fees from Chiesi, Dicerna and Alnylam outside the submitted work. L.Q. reports personal fees from Otsuka, Alexion and GlaxoSmithKline outside the submitted work. A.H. reports personal fees from Alexion outside the submitted work. M.P. reports personal fees from Otsuka, Alexion, Retrophin and Novartis outside the submitted work. The rest of authors declare no conflicts of interest.

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