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ORIGINAL ARTICLE

Extracapillary proliferation scoring correlates with renal outcome and contributes to stratification in adult patients with immunoglobulin A nephropathy

Jhonny L. Moreno[1], Lida M. Rodas[2,3], Juliana Draibe[1], Xavier Fulladosa[1], Montserrat Gomá[4], Adriana Garcia-Herrera[5], Josep M. Cruzado[1], Joan Torras[1,*] and Luis F. Quintana[2,3,*]

[1]Department of Nephrology, Bellvitge University Hospital, Barcelona, Spain, [2]Department of Nephrology and Renal Transplantation, Centro de Referencia en Enfermedad Glomerular Compleja del Sistema Nacional de Salud (CSUR), Hospital Clínic—University of Barcelona, Barcelona, Spain, [3]Department of Medicine, Institut d'Investigacions Biomédiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain, [4]Department of Pathology, Bellvitge University Hospital, Barcelona, Spain and [5]Department of Pathology, Centro de Referencia en Enfermedad Glomerular Compleja del Sistema Nacional de Salud (CSUR), Hospital Clínic—Department of Medicine, University of Barcelona, Barcelona, Spain

Correspondence to: Jhonny L. Moreno; E-mail: jhonnymoreno.acosta@gmail.com
*These authors share senior authorship.

ABSTRACT

Background. The revised Oxford classification of diagnostic renal biopsies has been proposed to aid in the prediction of renal outcome. We aimed to validate the histological crescents and interstitial fibrosis and tubular atrophy (IFTA) subgrouping, and to investigate the additional value of the proportion of crescents (CatPE) in the prediction of renal outcome.

Methods. Data were retrospectively collected over 10 years, from the time of diagnosis, by systematic review of medical records from 90 patients with renal biopsies recruited to cohorts from two hospitals in Spain. Patients were classified into three groups for the analysis: CatPE >25% (C2), CatPE <25% (C1) and without this type of lesion (C0). The end point was renal survival defined by either >50% reduction in glomerular filtrate rate or end-stage renal disease.

Results. Renal survival at 5 years was 90% in group C0, 81% in group C1 and 31% in group C2 ($P = 0.013$). The presence of >25% crescents in the sample was associated with more severe disease when compared with <25%, as demonstrated by more interstitial fibrotic change and by lower estimated glomerular filtration rate at diagnosis, as well as worse renal function at 2 and 5 years. At the time of diagnosis and at 24 months, the group with IFTA >50% had poorer renal function compared with the other groups.

Conclusions. We have confirmed the predictive value for renal survival of the revised Oxford classification in a two-centre study. We found worse renal outcome in patients with severe tubulointerstitial fibrosis and atrophy. Patients with

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extracapillary lesions >25% and IFTA >50% had a worse renal prognosis due to more severe kidney injury. These results contribute to patient stratification in immunoglobulin A nephropathy for therapeutic, epidemiological and basic research.

Keywords: CatPE, eGFR, extracapillary proliferation, glomerular filtration, IFTA, IgAN IgA nephropathy, interstitial fibrosis–tubular atrophy

INTRODUCTION

Iimmunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis in the world [1], with an overall incidence of at least 2.5/100 000 of people per year in the adult population [2] and a variable prevalence according to the geographical area. According to the Spanish registry of glomerular diseases (GLOSEN) its prevalence in Spain is between 13% and 15%.

The diagnosis requires a renal biopsy confirming the presence of IgA in the mesangium and glomerular capillaries [3].

Described for the first time in 1968 by Berger and Hinglais, it is characterized by the presence of intercapillary deposits of immune complexes formed *in situ* by IgA–IgG. This IgA is predominantly type 1 in its polymeric form and exhibits an aberrant glycosylation pattern characterized by galactose deficiency in the hinge region of the heavy chain. After an antigenic stimulus, immunocomplexes are generated and deposited in the mesangium, causing local inflammation, with the consequent production of different cytokines and complement activation. The local inflammatory response is variable and generates mesangial, endocapillary and interstitial cell proliferation, and in some cases extracapillary lesions [4–6].

Renal biopsy is not only useful for diagnosis but also allows patient categorization by the Oxford classification, which established mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S) and moderate-to-severe interstitial fibrosis and tubular atrophy (IFTA) (T) as independent risk factors for a poor renal outcome. In addition, the presence or absence of extracapillary lesions and their percentage must be specified [7].

KDIGO considered only very rare cases of rapidly progressive glomerulonephritis that resembles ANCA-associated vasculitis when crescents involve >50% of glomeruli [8]. However, most crescentic IgAN cases have <30% of crescents, the prognosis and treatment of which are uncertain. Crescentic lesions were not found to have a prognostic value in the Oxford and Validation study of the Oxford Classification for IgA nephropathy (VALIGA) studies, but there was a bias for using of steroids or immunosuppressive therapy in these patients [9]. Recently, an analysis that combined data from the Oxford, VALIGA, China and Japan cohorts demonstrated that crescents were predictive of a combined event, but only in patients not receiving immunosuppressive therapy. Extracapillary proliferation (CatPE) <25% increased the risk of a >50% decline in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD) in patients without immunosuppressive treatment, while crescentic lesions >25% increased the risk of eGFR decline or ESRD independent of treatment [10–13]. Hence, the revised Oxford classification suggests considering C1 (1–24% of glomeruli) and C2 (>25% glomeruli with crescents) as an independent and robust item for stratification.

We sought to validate the revised Oxford classification of IgAN for the prediction of renal outcome in an inclusive, two-centre Spanish cohort as opposed to a cohort selected from clinical trial recruits. We also sought to test the additional prognostic value of the number of crescents and to revisit the potential predictive role of the immunosuppressive treatment in this context.

MATERIALS AND METHODS

Study design

This was an observational, descriptive and retrospective study in 90 patients diagnosed with IgAN from two Spanish university hospitals. The inclusion criteria were biopsy-proven IgAN with pathology slides available for review, requiring a minimum of 10 glomeruli. All patients were diagnosed by renal biopsy at Clinic Hospital and Bellvitge University Hospital between 2005 and 2015. One patient was withdrawn due to incomplete data in the clinical history (1%).

Of note, the policy of both centres is that renal biopsy in patients with suspected IgAN is usually indicated in cases with microhaematuria and proteinuria >1 g/day in more than two determinations with or without associated renal dysfunction.

Patients and data

Patients were classified into three groups according to the Haas description: patients with extracapillary lesions (CatPE) >25% (C2), patients with CatPE <25% (C1) and patients with the absence of this type of lesion (C0). There were no restrictions on initial eGFR or proteinuria, and the length of follow-up was required to be 1 year, unless ESRD occurred before that time.

Patients <15 years of age, IgAN cases associated with post-infectious glomerulonephritis, systemic lupus erythematosus, ANCA-associated vasculitis, chronic liver disease and Henoch–Schonlein purpura were excluded.

Evaluation of clinical parameters

Data were collected on patients' characteristics at the time of renal biopsy and during follow-up, including demographics, BP, eGFR and proteinuria. Blood levels of C-reactive protein (CRP) and IgA were also recorded in units of milligrams per litre and grams per litre, respectively. Follow-up information was available on the use of renin–angiotensin system blocking drugs and immunosuppressive therapy.

We estimated the eGFR using the chronic kidney disease Epidemiology Collaboration (CKD-EPI). MAP was calculated as 1/3(systolic BP) + 2/3(diastolic BP). Immunosuppressive therapy after renal biopsy was defined as treatment with any immunosuppressive agent, regardless of duration or dose.

The outcomes were the rate of renal function decline (slope of eGFR) and renal survival from a combined event defined by either >50% reduction in eGFR or ESRD (eGFR 15 mL/min/1.73 m^2).

Histological review

Two pathologists scored the biopsies using the Oxford criteria. Mesangial proliferation was defined (M1 or M0) according to the presence of proliferation greater or less than 50% of the

Table 1. Clinical and demographic characteristics

Variables	Overall ($n = 89$)	C0 ($n = 51$)	C1 ($n = 21$)	C2 ($n = 17$)	P-value
Follow-up, months [mean (SD)]	52 (29)	54(24)	60 (39)	37 (25)	0.04
Male (%)	62 (69)	36 (70)	15 (71)	11 (64)	0.89
Age at diagnosis, years [median (interquartile range)]	45 (16–83)	45 (18–81)	48 (20–83)	42 (16–64)	0.5
eGFR at diagnosis, mL/min/1.73 m^2 [mean (SD)]	50 (33)	55 (32)	58 (30)	23 (26)	0.001
Proteinuria, g/day [mean (SD)]	3 (3.7)	3 (4.4)	2.6 (2)	3.4 (3)	0.052
HTA [*n* (%)]	68 (76)	40 (78)	15 (71)	13 (76)	0.64
IgA g/L [mean (SD)]	4.95 (1.88)	4 (1.2)	3.25 (1.4)	4.3 (3)	0.31
CRP, mg/L [mean (SD)]	16 (34)	12.1 (26)	21.3 (44)	23.6 (39)	0.45
Macrohaematuria [*n* (%)]	11 (12)	3 (5)	2 (9)	6 (35)	0.006

Kolmogorov–Smirnov test. C0, without CatPE, C1, CatPE <25%, C2, CatPE >25%. HTA, arterial hypertension.

glomeruli, defined as four or more cells in one or more mesangial areas. Endocapillary proliferation is described by the letter E; E1 specifies the presence of this parameter, E0 its absence. The third parameter was the segmental sclerosis, described by the letter S; S1 specifies the presence of this parameter, S0 its absence. The last histological parameter, IFTA, was divided into three categories: T1 ≤25%, T2 26–50% and >50% described as T3.

The recent modification of the Oxford classification on extracapillary lesion parameters was included. C1 describes the presence of extracapillary lesion, C0 its absence. In addition, the percentage of extracapillary lesions was recorded in four grades (0 = 0%, 1 = <25%, 2 = 26–50%, 3 = >50%). We determined the fraction of glomeruli with cellular or fibrocellular crescents. A crescent was defined as extracapillary proliferation of more than two cell layers of any size. A cellular crescent was defined by >50% of the lesion occupied by cells, and a fibrocellular crescent was defined by <50% of the lesion occupied by cells and <90% occupied by matrix. Fibrous crescents (composed of >90% matrix) were not considered [8–11].

Statistical analysis

Continuous and categorical variables are expressed as mean with standard deviation and number with percentage, respectively. To evaluate the normal distribution of the variable, the Kolmogorov–Smirnov test was performed. The variables with normal distribution used the mean as a measure of central tendency, and standard deviation as a measure of dispersion. The data with abnormal distribution were used as the median measure of central tendency and the interquartile range as a measure of dispersion. The comparison of two qualitative variables was performed using the Chi-square test. Student's *t*-test was used to compare a quantitative variable and qualitative dichotomous variable, while the ANOVA test was used to compare the quantitative variable with a non-dichotomous qualitative variable. Regression study used the Cox proportional hazard model and coefficients were expressed as a hazard ratio (HR) with a 95% confidence interval (CI). Renal survival was measured from the time of biopsy and was analysed using the Kaplan–Meier method, and the equality of survival functions was examined using the log rank test. We used Kaplan–Meier survival curves and Cox regression to test the relation between crescents, expressed in categories, and the survival from a combined event. The multivariate models addressed the predictive value of crescents adjusted for covariates (initial eGFR; time averaged MAP and proteinuria; and M, E, S and T lesions). Because the presence of crescents was strongly associated with the subsequent use of immunosuppression, we performed *a priori* each model for the entire cohort plus the untreated and treated groups separately.

Table 2. Histological variables

Oxford classification	Overall ($n = 89$)	C0 ($n = 51$)	C1 ($n = 21$)	C2 ($n = 17$)	P-value
M1 [*n* (%)]	76 (85)	41 (80)	19 (90)	16 (94)	0.7
E1 [*n* (%)]	22 (24)	8 (15)	5 (23)	9 (52)	0.008
S1 [*n* (%)]	20	19	27	16	0.2
IFTA					0.38
T0 [*n* (%)]	12 (13)	9 (17)	3 (14)	0	
T1 [*n* (%)]	41 (46)	23 (45)	9 (42)	9 (52)	
T2 [*n* (%)]	19 (21)	8 (15)	5 (23)	6 (35)	
T3 [*n* (%)]	18 (20)	11 (21)	5 (23)	2 (11)	

E1, endocapillary proliferation; S1, glomerular sclerosis; M1, mesangial proliferation.

All P-values were two-tailed and were considered significant when <0.05. Analyses were carried out using SPSS (version 22; IBM SPSS, Chicago, IL, USA) and the R software (version 3.1.2; Free Software Foundation).

RESULTS

Clinical baseline characteristics of the cohort

The main baseline characteristics of the patient cohort are summarized in Table 1. The mean age was 45 years (16–83 years), with a predominance of males (62, 69%). Macrohaematuria was present in 11% and was more frequent in group C2. Seventy-six percent of the patients presented arterial hypertension at the time of diagnosis. The mean proteinuria of the study population was 3 g/day, and there was a trend of higher proteinuria in the group C2. There were no differences in IgA and CRP levels among the groups with different degrees of CatPE.

Strikingly, there were differences in renal function at diagnosis related with the presence of CatPE >25%; the mean of eGFR was 23 mL/min/1.73 m^2 in group C2; 58 mL/min/1.73 m^2 in C1; and 55 mL/min/1.73 m^2 in C0 (P = 0.001). There were no differences in renal function between C1 and C0 group (P = 0.97, 95% CI −22 to 16).

Regarding treatment, the renin–angiotensin aldosterone system blockers were used in 65.1% of patients, and immunosuppression was started in 45% of the patient cohort.

Renal biopsy findings

Regarding histological variables, the mean number of glomeruli in the sample was 12. A total of 38 (49%) patients had the

presence of extracapillary lesions. Table 2 shows the distribution of the MEST criteria of the Oxford classification in relation to the percentage of crescents observed in the three groups of the study population.

Cellular and/or fibrocellular crescents were present in 38 individuals. The presence of crescents correlated with the E lesion (odds ratio of E concurrent with any crescents, 5.8; 95% CI 4.4–7.4; P = 0.008). All the patients in the C2 subgroup had some grade of IFTA.

Renal outcomes

As reported, at diagnosis, group C2 presented lower GFR compared with C1 or C0. In the same line, at 60 months after diagnosis, the mean of eGFR was 15 mL/min/1.73 m^2 in group C2 compared with 59 mL/min/1.73 m^2 in CatPE <25% (Groups C0 + C1) (P = 0.035, 95% CI 1.4–40).

Interestingly, at 60 months, patients included in group C2 presented a doubled risk for ESRD compared with CatPE <25%, while IFTA >50% increased five times the risk of ESRD compared with IFTA <50%. Neither proteinuria, macrohaematuria nor endocapillary proliferation was an additional risk factor for ESRD among the comparison groups (Table 3).

Table 3. Variables associated with poor renal prognosis

Variable	HR (95% CI)	P-value
Proteinuria	0.6 (0.3–1.2)	0.19
Macrohaematuria	3 (0.9–9)	0.052
IFTA >50%	4.9 (1.1–20)	0.03
Endocapillary proliferation	1.4 (0.3–6)	0.6
CatPE >25%	2.1 (1–4.5)	0.03

The multivariable Cox regression model.

Figures 1 and 2 show that there was an inverse relationship between the percentage of CatPE and renal survival. While renal survival was better when CatPE was <25%, and there were no differences between the groups with CatPE 26–50 and >50%. Renal survival at 5 years was 83% in the group with CatPE <25% (C0 + C1) and 40% in the group C2 (P = 0.001). The presence of >25% crescents in the sample was associated with more severe disease when compared with <25%, as demonstrated by more interstitial fibrotic change and by lower GFR at diagnosis, as well as worse renal function at 2 and 5 years. At the time of diagnosis and at 24 months, the group with IFTA >50% had worse renal function compared with the other groups (Levene's statistic of 9.5 and 7.1, P = 0.005 and P = 0.001) (Table 4).

Figure 3 shows the difference in renal survival at 60 months follow-up in patients with IFTA >50% compared with the group with lesions <50%.

In multivariate analysis with respect to renal survival (Table 5), the CatPE >25% contributed a 21% increased likelihood of the event advanced kidney disease (P = 0.001) and IFTA >50% contributed a 28% increase (P = 0.009).

Immunosuppression

Regarding the immunosuppressive therapy, mono-therapy with corticosteroids was prescribed in 19% of the patients with extracapillary lesion; corticosteroids plus other drugs were administered in 44.2% of the individuals. The use of these medications was higher in group C2 (Table 6). The great

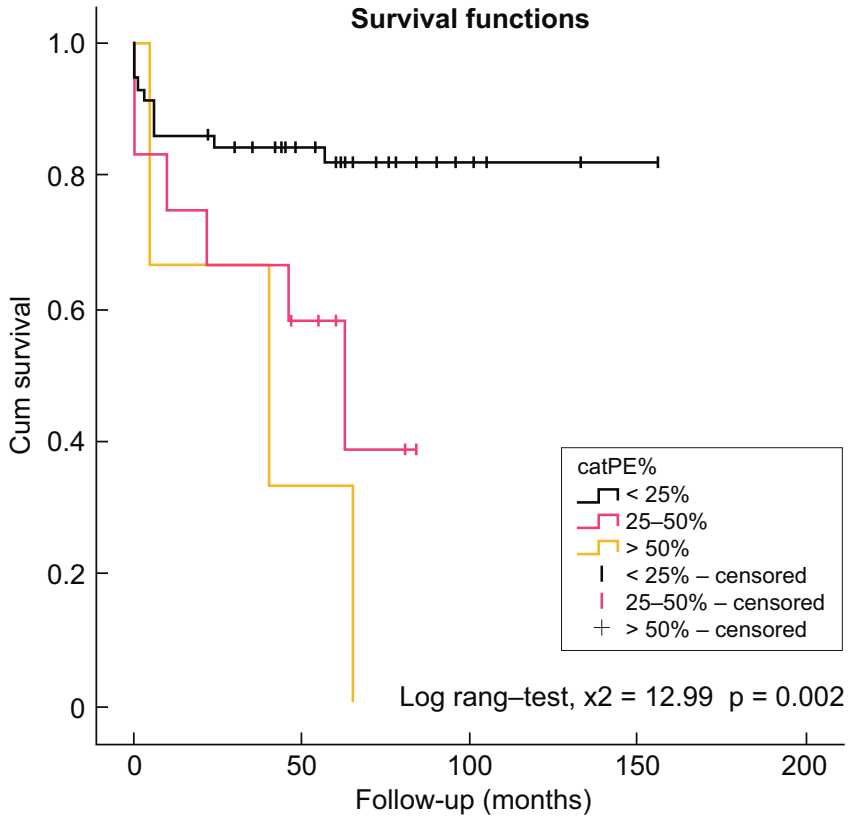

FIGURE 1: Kaplan–Meier survival curve with the three degrees of CatPE.

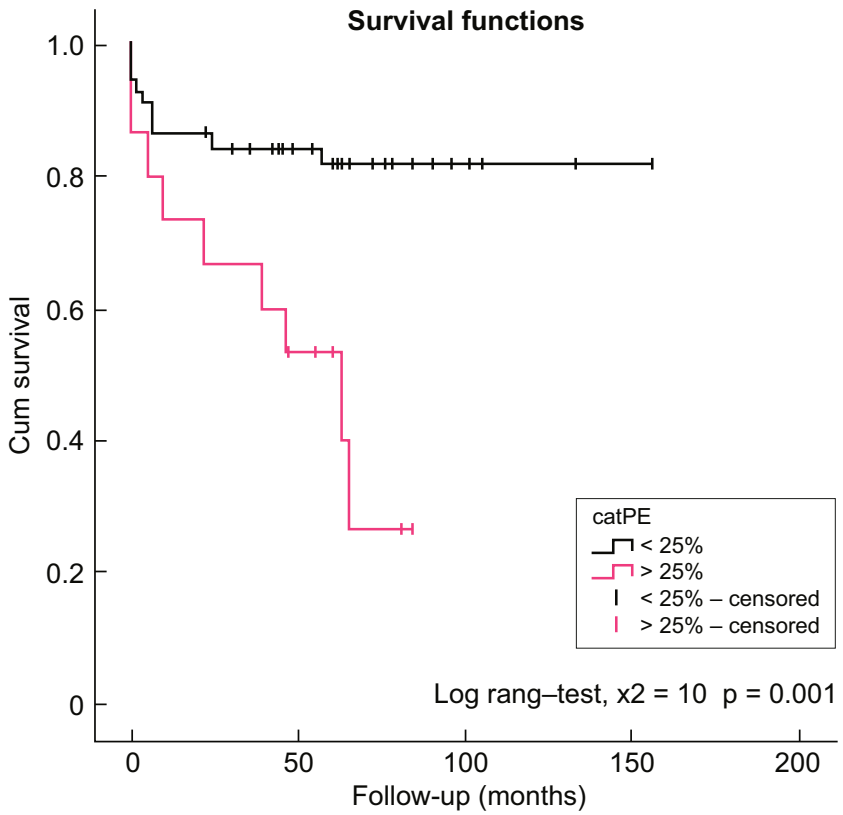

FIGURE 2: Kaplan–Meier survival curve in relation to degree of CatPE.

Table 4. Comparison of the degree of IFTA with renal function at diagnosis and after 24 months of follow-up

eGFR[a]	IFTA (%)	*n*	Mean (SD)	95% CI	P-value
Diagnosis	<50	69	56 (34)	19–41	0.001
	>50	18	26 (14.6)		
24 months	<50	57	59 (34.5)	24–47	0.002
	>50	17	23 (22.9)		

[a]eGFR (mL/min/1.73 m^2). Student's *t*-test.

majority of the group with extracapillary lesions >25% received treatment with cyclophosphamide or plasma exchange, and the difference was statistically significant with respect to cyclophosphamide (P = 0.004). In patients not treated with immunosuppression, addition of crescents improved the ability of the model to discriminate between patients who did or did not experience the event 5 years after biopsy (P = 0.05). In contrast, there was no improvement to the discrimination performance by adding crescents to the model in patients receiving immunosuppressive therapy.

DISCUSSION

IgAN is an important cause of ESRD in young adults, with broad clinical and histological variability and uncertain prognosis. Furthermore, the phenotype of renal involvement in IgAN has a major influence on survival, and the revised Oxford classification of diagnostic renal biopsies has been proposed to aid in the prediction of renal outcome. Crescents are the histological hallmark of rapid progression and severity in many glomerular diseases. However, in IgAN their predictive value and therapeutic significance are still unclear.

We aimed to validate this histological subgrouping and investigate the additional value of the proportion of crescents in the renal biopsy for the prediction of renal outcomes in 89 patients from cohorts of two hospitals in Spain.

In common with observations by Haas *et al.* [10], our study found that the extracapillary lesion is an independent factor of worse renal prognosis at diagnosis and during follow-up to 60 months. This risk of renal dysfunction increased when extracapillary lesions were in >25% of the glomeruli. This finding was similar to that found in the studies by Serriello *et al.* [14]. Contrary to our results, the studies published by Lee *et al.* [15] and Zhang *et al.* [16] did not find that extracapillary lesions were an independent factor of poor renal prognosis, possibly because their patient population had a milder disease phenotype.

In relation to the other histological variables included in the MEST Oxford classification, we found that only the degree of IFTA >50% was associated with poor renal prognosis. Regarding glomerular sclerosis and the presence of endocapillary proliferation, considered in previous studies as histological parameters of poor prognosis [17, 18], our study found no correlation between these parameters and renal function at the time of diagnosis and after 60 months of follow-up. The other histological parameters showed no statistically significant differences either. This study confirms previously described observations on the impact of IFTA on short- and long-term renal survival. The presence of an IFTA grade >50% was associated with a poor renal outcome [19, 20].

These findings from the Spanish population are in agreement with the last paper from the VALIGA study [21], which

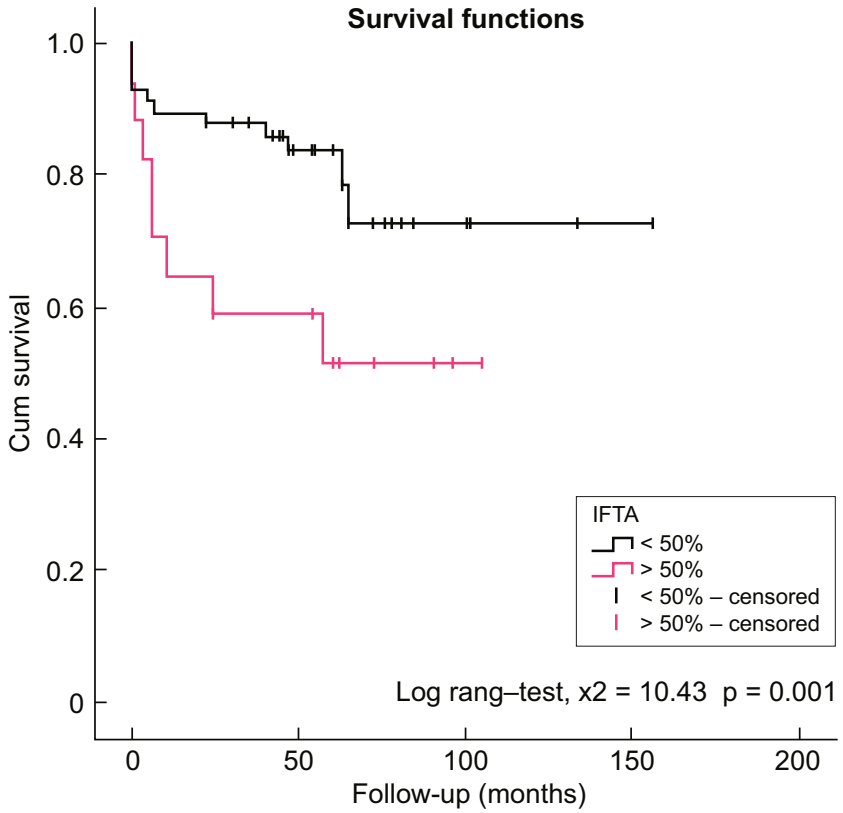

FIGURE 3: Kaplan–Meier survival curve in relation to the degrees of IFTA.

Table 5. Independent variables of poor renal prognosis

			95% CI Exp. (B)	
Variable	Significance	Exp. (B)	Lower	Upper
CatPE >25%	0.001	0.213	0.085	0.534
IFTA >50%	0.009	0.289	0.114	0.732

Multivariate Cox regression analysis.

Table 6. Immunosuppressive therapy

	Overall ($n = 90$)	C0 ($n = 51$)	C1 ($n = 21$)	C2 ($n = 17$)
No treatment IS [*n* (%)]	49 (55)	37 (72)	10 (47)	2 (11)
Corticosteroid monotherapy [*n* (%)]	17 (19)	9 (17)	5 (9)	3 (17)
Mycophenolate [*n* (%)]	13 (14)	5 (9)	4 (19)	4 (23)
Cyclophosphamide [*n* (%)]	11 (12)	0	3 (14)	8 (47)

stated that extracapillary lesion was associated with worse renal function during follow-up, finding a worse prognosis in the group of patients without immunosuppressive treatment. The presence of mild-and-moderate IFTA (T1 and T2) was also an independent factor of loss of renal function at 5 years of follow-up. However, this is a rather severe cohort of IgAN patients given that 43% presented crescents compared with 10.5% in the VALIGA cohort [21].

Contrary to the results from Tan *et al.* [22], the use of immunosuppressive treatment in our cohort was not associated with better renal function at 60 months of follow-up. This may be explained by the presence of patients in our cohort with worse renal function at diagnosis and with a greater percentage of extracapillary lesions compared with those in previously mentioned studies.

Based on all the findings confirmed in this Spanish cohort, it seems sensible to include the precise quantification of cellular crescents in the routine evaluation of the biopsy of patients with IgAN, since it constitutes an independent prognostic factor of renal survival after 2 years of the diagnosis. The evaluation of the presence of cellular crescents in the renal biopsy is a procedure very dependent on the quality of the histological preparation and the experience of the renal pathologist. According to the study by Bellur *et al.* [21], there is disagreement when classifying the histological lesions of the MEST terms among pathologists from different centres, especially with regard to the parameters of glomerular sclerosis and active extracapillary lesion. On the contrary, the presence of lesions M1, E1, C1 and S1 was associated with the decision to treat with steroids, resulting in better outcomes for the group of treated patients.

In order to optimize the therapeutic window guided by renal biopsy, it would be highly advisable to have an objective and rapid method of digital pathology that allows a more objective quantification of the number of cellular crescents.

An adequate characterization of extracapillary proliferative lesions, in addition to the criteria of the revised Oxford classification, would allow a pathology-based approach to IgAN. This strategy is a step forward towards an objective evaluation of the impact of immunomodulatory treatments using a control biopsy during the follow-up and its influence on the appearance of advanced chronic disease in this group of patients. The previously described observations on the impact of IFTA on short- and long-term renal survival were confirmed by our study [19].

In this work, treatment received after the diagnosis was not considered when looking at long-term renal survival, but differences in practice in the choice and duration of therapy between centres was small. Information about follow-up renal biopsies in IgAN is scarce, but it seems that therapy could facilitate the partial reversal of active lesions; since chronicity progresses despite treatment, the treatment received by the patients in the study was likely to have influenced renal outcomes. The study is limited by its retrospective design and data collection from two centres. Although histopathological parameters on renal biopsies were assessed by experienced pathologists following a scoring protocol developed for IgAN, inter-observer variation was not assessed. However, this has also been determined in previous studies. Inter-observer variation for the classification into the three categories of crescents was not assessed either.

CONCLUSIONS

In conclusion, this work shows that the classic parameters of poor prognosis in IgAN, such as proteinuria, hypertension at diagnosis and age, are markers that have a lower weight when histological lesions are well characterized. This highlights the importance of renal biopsy not only for early diagnosis, but also to enable individualized treatment to be administered to patients with IgAN. Possibly, the detailed study of renal biopsy associated with the measurement of IgG antibodies against hypogalactosidated IgA and complement proteins may constitute the future panel of prognostic biomarkers in IgAN.

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CONFLICT OF INTEREST STATEMENT

None declared.

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