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ORIGINAL ARTICLE

Could mesangial C3 deposition be an independent prognostic marker in immunoglobulin A nephropathy?

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Abstract

Background Immunoglobulin A nephropathy (IgAN) is a common primary glomerulonephropathy. There is evidence that mesangial C3 deposition plays a role in the development of the disease. The aim of this study was to examine the effect of C3 deposition on the prognosis of IgAN patients.

Method The study included 1135 patients with biopsy-confirmed IgAN from the database of the Turkish Nephrology Association Glomerular Diseases Working Group (TSN-GOLD). Patients were excluded from the study if they were aged < 18 or > 75 years or if C3 staining had not been performed in the immunofluorescent analysis. C3 deposition was defined as an immunofluorescence intensity of C3 ≥ 2 + within the mesangium. The primary endpoints were the development of end-stage renal disease, a 30% decrease in glomerular filtration rate compared to the basal value or an elevation in proteinuria to a nephrotic level (3.5 gr/day).

Results Mesangial C3 deposition was observed in 603 (53.1%) patients. No statistically significant difference was found at baseline between the groups with and without mesangial C3 deposition, as for age, sex, BMI, proteinuria level, or the presence of hypertension. In the follow-up period with a mean duration of 78 months, no significant difference was found between the two groups regarding the primary endpoints ($p = 0.43$). A significant correlation between C3 deposition and segmental glomerulosclerosis (S1) according to the Oxford MEST-C classification was found ($p = 0.001$).

Conclusion Although a correlation was observed between mesangial C3 deposition and the S1 MEST-C classification, mesangial C3 deposition was not a prognostic factor in IgAN.

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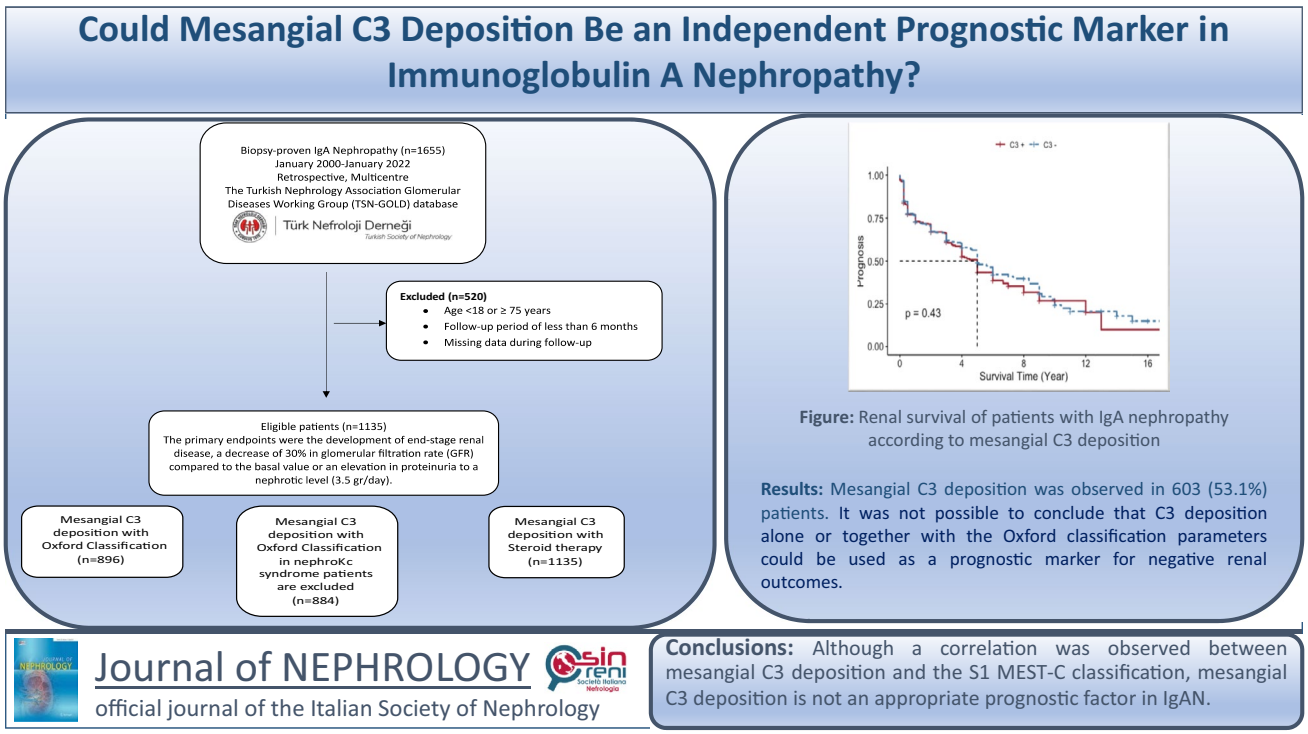
Graphical abstract



Keywords IgA nephropathy · Complement · C3 deposition · Oxford classification

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide [1]. The annual incidence of IgAN in Europe is estimated to be 2.5 cases per 100,000 adults [2]. Spontaneous remission can occur [3]. The geographic distribution of the disease suggests a genetic predisposition; a higher prevalence is seen in Asian countries than in Europe [4].

IgAN pathogenesis has still not been fully clarified [5]. IgAN is characterized by varying concentrations of IgG and/or IgM, which can accompany IgA deposition in the glomerular mesangium. Complement 3 (C3) granular deposition may also accompany expansion in the matrix and mesangial proliferation that occur concurrently with the disease. The process causing IgA deposition is thought to initiate with abnormal IgA glycosylation leading to immune complexes containing dimeric or polymeric IgA1 with impaired glycosylation accumulating in the mesangium. The complement system is thought to be involved in this process [4].

Although hypertension, increase in proteinuria and decrease in glomerular filtration rate may indicate a need for treatment, this point is still controversial. The Oxford classification is recommended by the Working Group of the International IgA Nephropathy Network and the Renal Pathology Society to predict prognosis and plan treatment [6]. The Oxford classification is based on the findings of light microscopy. The Oxford MEST classification was defined in 2009 as mesangial hypercellularity (M1), endocapillary hypercellularity (E1), segmental glomerulosclerosis (S1), and tubulointerstitial fibrosis (T1-2). This was updated to the MEST-C classification with the addition of crescentic lesions (C1-2) [7].

Specific exogenous antigens that could cause IgAN have not yet been determined. It is thought that food antigens such as casein and gluten could trigger the disease [8]. IgAN is often exacerbated by upper respiratory tract or gastrointestinal system infections. Glycosylation changes in IgA1 structure play a key role in the development of the disease. Immune complexes formed from O-glycosylated IgA1 in an abnormal polymeric way accumulate in the mesangium [9]. Some studies show that the complement system plays a role in the pathogenesis of IgAN: the alternative complement pathway and the lectin pathway have been found to be activated in patients with IgAN [8].

An increase in complement activation is caused by nephritogenic immune complexes containing IgA1, worsening kidney damage [8]. Furthermore, some

previous studies have suggested that mesangial C3 deposition could be a marker of poor prognosis [10]. Although some studies have found a correlation between the Oxford classification and the decrease in glomerular filtration rate with C3 deposition, other studies were not able to confirm this association [11].

This study aimed to further examine the effect of C3 deposition on the prognosis of IgAN patients, in a large multicentre cohort.

Materials and methods

Ethics statement

This retrospective study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12]. Approval for the study was granted by the Ethics Committee of Istanbul University Faculty of Medicine (Number: 09/28.06.2011).

Population and setting

The Turkish Nephrology Association Glomerular Diseases Working Group (TSN-GOLD) database was used for this study. Multicentre data were evaluated retrospectively. The study included the data of 1135 patients with biopsy-confirmed IgAN, followed up in different centres between January 2000 and January 2022. Patients were excluded if they were aged < 18 years or > 75 years, did not have C3 staining performed during the immunofluorescence microscopic examination or were followed up for less than 6 months.

Measurements and definitions

The demographic, clinical, and biochemical data of the patients were obtained from the TSN-GOLD database. Age, sex, blood pressure, body mass index, serum lipid levels, microscopic haematuria, and calculated glomerular filtration rate were recorded as the baseline data. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Microscopic haematuria was defined as a count of ≥ 5 red blood cells per microscopic area in the urine sediment. The glomerular filtration rate was calculated using the Chronic Kidney Disease Collaboration (CKD-EPI) equation for estimated glomerular filtration rate (eGFR) [13]. The biochemical values obtained included blood urea nitrogen, serum creatinine, haemoglobin, serum albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and C3 and complement 4 (C4) levels. Follow-up data of blood pressure, 24-h urine protein excretion, and eGFR were recorded at visits at 3-month intervals. Kidney biopsy samples were evaluated according to the Oxford classification. Immunofluorescence staining intensity was reported on a scale of 0–3 +, with 0 representing negative staining; 1 +, low-intensity staining; 2 +, medium-intensity staining; and 3 +, high-intensity staining. C3 deposition was defined as an immunofluorescence intensity of C3 ≥ 2 + [14]. Crescentic lesions were defined as CO, C1, or C2 according to the Oxford MEST-C classification [7]. Data on renin-angiotensin system inhibitor (RASi) and steroid use were recorded. Steroid treatment was defined as treatment with at least 0.5 mg/kg/day prednisolone or equivalent for at least one month.

Follow-up and outcome

Renal survival time was defined as the time from biopsy to transition to renal replacement therapy, end-stage kidney disease (ESKD), or the final follow-up visit [15, 16].

Statistical analyses

Patient data was analysed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA), and R software was used for data visualization. Conformity of the data to a normal distribution was assessed with visual (histogram and probability graphs) and analytical methods (Kolmogorov−Smirnov/Shapiro−Wilk tests), and parametric and nonparametric tests were applied accordingly. Continuous variables with a normal distribution are presented as the mean ± standard deviation (SD), and data with a skewed distribution are presented as median values and interquartile range. Categorical variables are presented as number (n) and percentage (%). Continuous variables were compared using the independent samples *t* test or the Mann−Whitney *U* test when parametric assumptions were not met. For categorical variables, the Chi-square test or Fisher's exact test when the number of data points was < 5 were applied.

Spearman and Pearson correlation tests were used to determine correlation between parameters. Logistic regression analysis was performed to determine the correlation between mesangial C3 deposition and the Oxford MEST-C classification. Univariate analysis was applied first, and variables showing a significant relationship with C3 deposition were included in the multivariate analysis.

Renal survival was defined as the time from biopsy to the onset of ESKD or the final follow-up visit. Survival rates were calculated using Kaplan−Meier survival analysis. To determine the relationship between patients with and without C3 deposition and the Oxford-MEST-C classification when there was a decrease of 30% in eGFR or the development of proteinuria of > 3.5 gr/day, a Cox proportional hazards

model was employed. The goodness of fit of the model was determined with the Hosmer−Lemeshow test. In all the analyses, $p < 0.05$ was considered statistically significant.

Results

Demographic data and baseline characteristics of the patients

A total of 1655 patients diagnosed with IgAN were evaluated. Of these, 498 were excluded because the follow-up period was shorter than 6 months, and 22 were excluded because there were no data on mesangial C3 staining. The study flowchart is shown in Fig. 1. The baseline characteristics of 1135 patients analysed and sorted according to mesangial C3 deposition are shown in Table 1. The 1135 patients included in the study comprised 699 (61.6%) males and 436 (38.4%) females with a mean age of 39.79 ± 12.68 years and a median eGFR of 71.12 (44.21–107.43) ml/min/1.73 m^2. No significant differences were found between patients with and without C3 deposition regarding age, sex, BMI, proteinuria level, renin-angiotensin system inhibitor (RASI) use and hypertension. Significant microscopic haematuria positivity and low levels of haemoglobin and eGFR were observed in the group with positive mesangial C3 deposition.

Pathological evaluation according to the Oxford classification was performed in 896 patients. In the C3-positive group, a significantly higher number of patients were classified as S1, T1, and T2. There was no significant difference between the groups regarding M1, E1, or the presence of crescents. Patients with clinical nephrotic syndrome at baseline were excluded, leaving for the analysis a total of 885 patients with a mean age of 38.95 ± 12.36 years, upon which a further statistical evaluation was focused. A significantly greater number of patients were classified as S1, and the mean 24-h urine protein level decreased to 2314 (2130–2497) mg/day (Table 5). Patients with acute kidney injury (AKI), rapid progression of glomerulonephritis and high levels of proteinuria were considered at high risk at the time of diagnosis. In a further subgroup analysis we

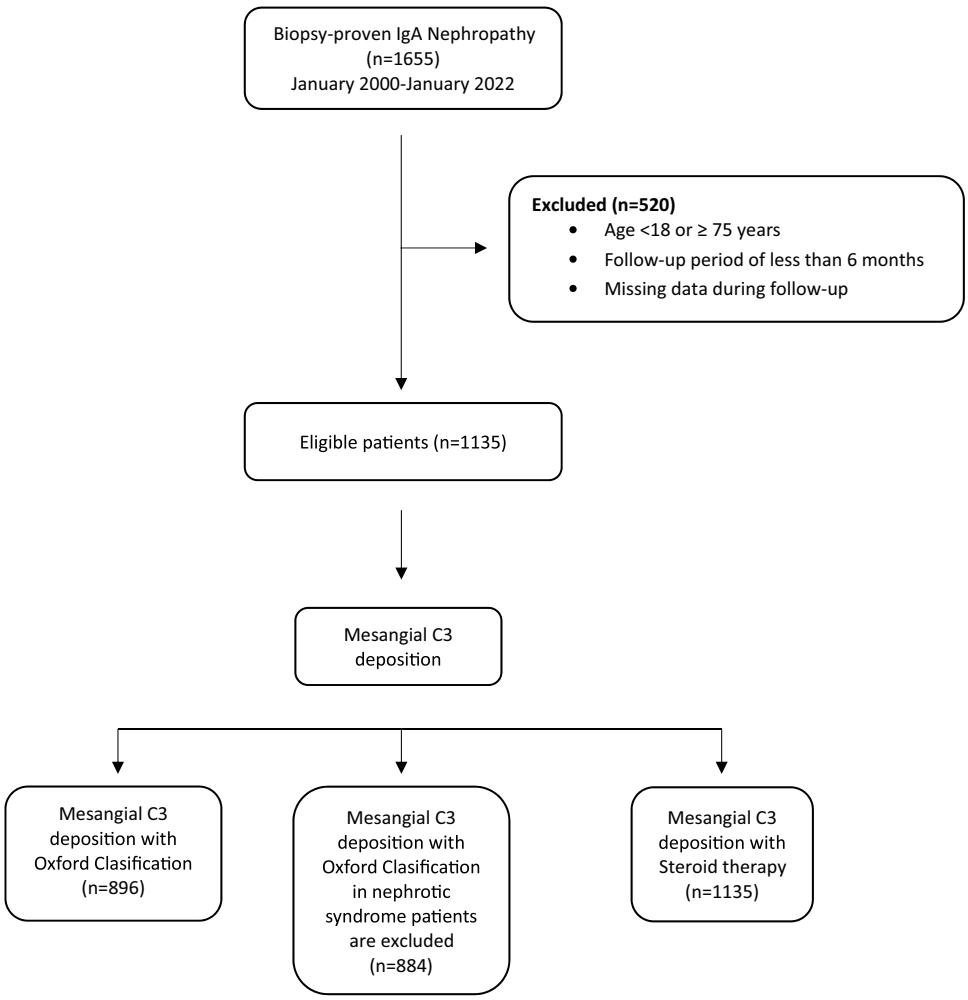


Fig. 1 Flow diagram of the study

Table 1 Baseline characteristics according to mesangial C3 deposition

Variables	Total ($n=1135$)	C3 deposition		p
		C3 negative ($n=532$)	C3 positive ($n=603$)	
Age (years)	39.79 ± 12.68	39.08 ± 12.36	40.36 ± 12.93	0.720
Male (%)	699 (61.6%)	315	384	0.122
Body mass index (kg/m^2)	26.12 (23.51–29.34)	26.29 (23.45–30.26)	25.97 (23.63–29.04)	0.325
Hypertension (%)	396 (34.9%)	191	205	0.458
Systolic blood pressure (mmHg)	133.74 ± 20.05	134.66 ± 20.81	133.01 ± 19.43	0.523
Diastolic blood pressure (mmHg)	82.40 ± 11.34	82.81 ± 11.34	82.06 ± 11.35	0.093
Microscopic hematuria (%)	808 (71.2%)	346	462	**< 0.001**
eGFR (ml/min/1.73 m^2)	71.12 (44.21–107.43)	80.53 (51.30–115.90)	64.16 (38.71–100.83)	**0.002**
BUN (mg/dL)	20 (14–30)	18 (12–27)	22 (15–31)	**< 0.001**
Hemoglobin (g/dL)	13.04 ± 2.08	13.21 ± 2.06	12.91 ± 2.08	**0.048**
Proteinuria (mg/day)	2708.51 (2540.82–2876.21)	2840.14 (2548.30–3131.97)	2592.71 (2409.46–2775.96)	0.352
Albumin (g/dL)	3.81 ± 0.66	3.79 ± 0.76	3.82 ± 056	0.763
Total cholesterol (mg/dL)	218.26 (213.27–223.24)	221.59 (213.12–230.07)	215.57 (209.68–221.45)	0.117
Triglyceride (mg/dL)	185.88 (175.67–196.09)	187.91 (173.46–202.37)	184.25 (169.88–198.61)	0.130
RASi use	741 (65.2%)	368 (69.2%)	373 (61.8%)	0.229
Oxford classification ($n=896$)				
M1 (%)	675 (59.5%)	284 (53.4%)	391 (64.8%)	0.145
E1 (%)	235 (20.7%)	96 (18%)	139 (23.6%)	0.349
S1 (%)	479 (42.2%)	181 (33.6%)	298 (49.4%)	**< 0.001**
T1 (%)	413 (36.4%)	188 (35.3%)	225 (37.3%)	**< 0.001**
T2 (%)	72 (6.3%)	25 (4.7%)	47 (7.8%)	**< 0.001**
Crescent C1 (%)	116 (10.2%)	46 (8.6%)	70 (11.6%)	0.132
Crescent C2 (%)	14 (1.2%)	9 (1.7%)	5 (0.8%)	0.132

Statistical significance is set at $p < 0.05$ (in bold)

Data are presented as mean ± SD, median (interquartile range) or n (%)

excluded high-risk patients, defined as those with proteinuria (> 2000 mg/day), eGFR < 60 ml/min/1.73 m^2 or AKI at the time of diagnosis. A total of 391 patients had a mean 24-h urine protein level of 1030.61 mg/day, mean age of 36.57 ± 11.88 years and mean eGFR of 103.60 ± 30.2 ml/min/1.73 m^2 (Table 6).

Correlations and survival analyses

Renal survival at 6 months was 83.8% in the overall study group, 82.8% in the C3-positive group, and 84.7% in the C3-negative group; at 5 years of follow-up, these rates were 53.8%, 50.7%, and 56.3%, respectively. The mean follow-up period was 26.62 (IQR: 6–36) months. The number of patients reaching the primary endpoint was 455 (40.1%) in the total sample, 215 (40.4%) in the C3-negative group and 240 (39.8%) in the C3-positive group. The mean renal survival was determined to be 78.45% (IQR: 70.67–86.24%) in the total sample, 74.82% (IQR: 62.45–87.19%) in the C3-positive group, and 80.65% (IQR: 70.47%-90.82%) in the C3-negative group ($p=0.430$) (Table 2, Fig. 2). When patients with nephrotic syndrome were excluded, the number of patients who reached the primary endpoint was 328 (37.1%) in the total sample, 143 (37.4%) in the C3-negative group and 185 (36.9%) in the C3-positive group. In a furtherr subgroup analysis, excluding the high-risk patients, the number of patients who reached the primary endpoint was 105 (26.9%) in the total sample, 50 (28.6%) in the C3-negative group and 55 (25.5%) in the C3-positive group.

Correlations between mesangial C3 deposition and the Oxford-MEST-C classification were examined using multivariate logistic regression analysis (Table 3). The results showed that the probability rate of C3 deposition was only significantly related to the classification of S1 [OR 1.72 (95% CI 1.27–2.32), $p=0.001$)].

Using the multivariate Cox model, no relationship was found between C3 deposition and the primary endpoints ($p=0.43$). In the subgroup analyses, when the patients with clinical nephrotic syndrome at the time of diagnosis were excluded, C3 deposition was not seen to have any negative effect on prognosis ($p=0.55$). Similarly, no significant relationship was determined between the primary endpoints and the presence of C3 staining with the M1,

Table 2 Renal survival analysis

Variables	Total ($n=1135$)	C3 deposition		p
		C3 negative ($n=532$)	C3 positive ($n=603$)	
Survival (%)				
3 months	96.6%	96.2%	96.8%	
6 months	83.8%	82.8%	84.7%	
1 year	76.9%	76.9%	76.8%	
2 years	71.1%	71.5%	70.7%	
5 years	53.8%	50.7%	56.3%	
Mean survival months (95% CI)	78.45 (70.67–86.24)	74.82 (62.45–87.19)	80.65 (70.47–90.82)	0.430

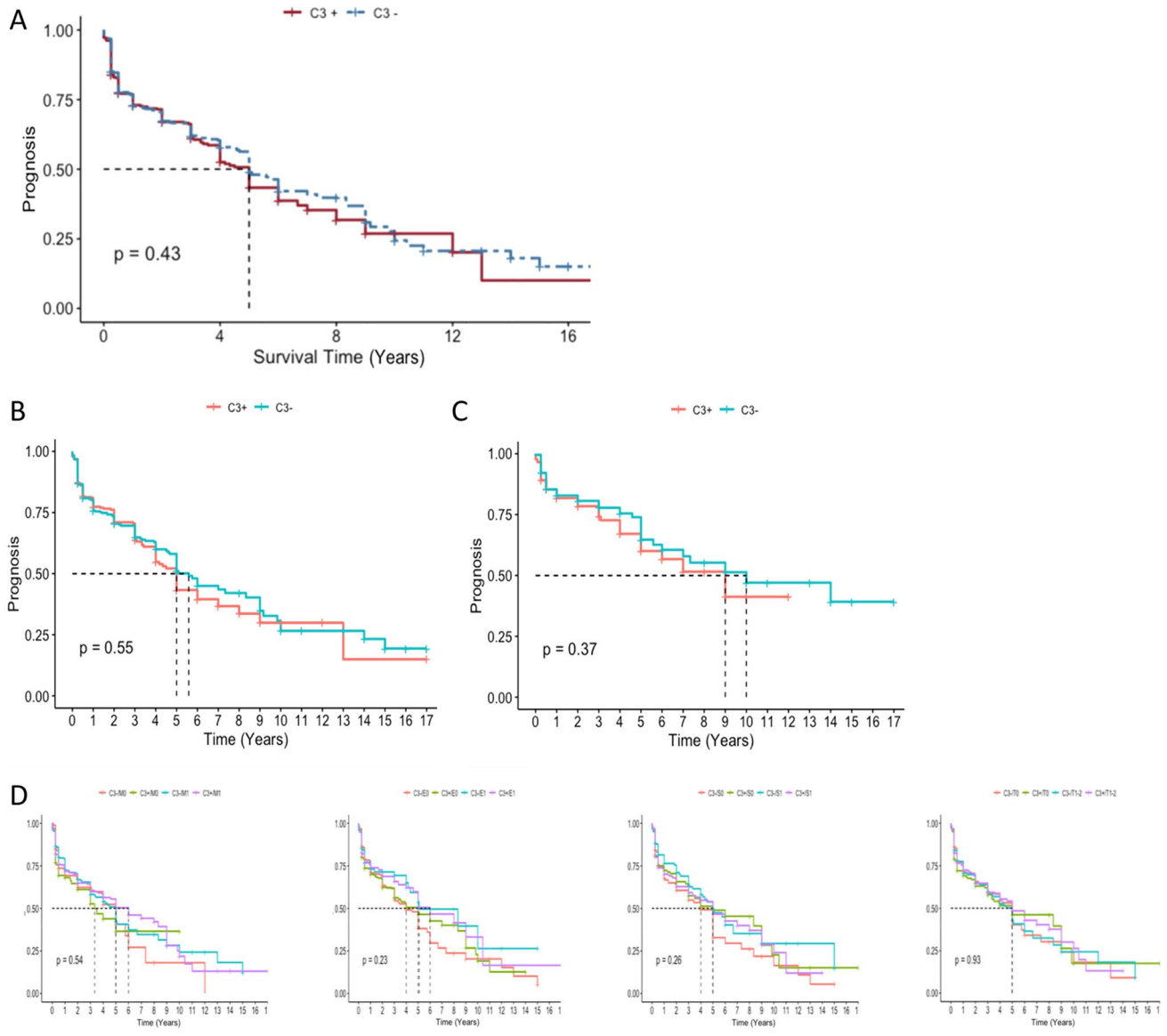


Fig. 2 Adjusted Kaplan-Meier analyses of cumulative renal survival of patients with IgA nephropathy according to mesangial C3 deposition (**A**) All patients, (**B**) Nephrotic syndrome patients are excluded (**C**) High risk patients excluded (**D**) MEST according to mesangial C3 deposition

E1, S1, T1-2, and C1-2 parameters of the Oxford classification ($p=0.54$; $p=0.23$; $p=0.26$; $p=0.93$; and $p=0.26$, respectively). Furthermore, in a further subgroup analysis excluding high-risk patients, C3 deposition had no significant effect on prognosis ($p=0.37$).

Combined effects of mesangial C3 deposition and the Oxford classification with steroid treatment on IgAN

The hazard ratio (HR) was evaluated considering the primary endpoint, which was a decrease of 30% in eGFR or persistent proteinuria > 3.5 gr/day during follow-up; according to age, sex, C3 staining, and the Oxford-MEST-C classification; and according to groups receiving and not receiving steroid treatment. In all the patient groups, the HRs for M1, E1, S1, T1-2, and C3 deposition were determined to be 0.99 (95% CI 0.75–1.30; $p=0.959$), 1.07 (95% CI 0.83–1.38; $p=0.568$), 0.87 (95% CI 0.69–1.11; $p=0.280$), 1.44 (95% CI 1.12–1.84; $p=0.004$), 2.89 (95% CI 1.94–4.30; $p<0.001$), and 0.92 (95% CI 0.73–1.16; $p=0.498$), respectively (Table 4).

Table 3 Multivariable-adjusted logistic regression analysis for mesangial C3 deposition according to the Oxford classification

Oxford classification	Odds ratio (95% CI)	*p* value
M1	1.26 (0.89–1.80)	0.184
E1	1.24 (0.89–1.72)	0.196
S1	1.72 (1.27–2.32)	**< 0.001**
T1-2	1.16 (0.89–1.51)	0.259
Crescent C1-C2	1.11 (0.73–1.70)	0.611

Statistical significance is set at $p < 0.05$ (in bold)

Discussion

In this multicentre, retrospective study, a large cohort of IgAN patients was evaluated. We investigated the relationship between C3 deposition and deterioration of kidney function and/or increase in proteinuria during follow-up. C3 deposition was analysed in combination with the widely used Oxford classification. Recent studies have concluded that the evaluation of C3 deposition alone or together with the Oxford scoring system parameters can predict poor prognosis [10, 14, 17]. In contrast to these findings, other studies have shown that besides C1q staining, all immune depositions included in immunofluorescence examinations have no effect on prognosis [11]. As the aetiology of the disease has not yet been fully clarified and there are geographical differences, the aim of this study was to investigate whether similar results could be achieved in our patient population. With this aim we analysed the effect of mesangial C3 deposition on survival and prognosis, the effect of C3 deposition together with the Oxford classification parameters, and finally the effect of the use of steroid treatment together with C3 deposition and the Oxford classification parameters. We conclude that C3 deposition, analysed alone or together with the Oxford classification, can be used as prognostic markers for adverse renal outcomes (Tables 5 and 6).

Mesangial C3 deposition was present in 53% of the study patients, and C3 deposition was unrelated to prognosis. A correlation between C3 deposition and serum creatinine levels was first reported by Nasri et al. [10], and Kim et al. reported that mesangial C3 deposition was an independent risk factor for progression [14]. Nam et al. stated that mesangial C3 and C4d deposition was associated with an increased risk of disease progression and that the predictive power of C3 was superior to that of C4d [18]. In those studies, the

Table 4 Hazard ratios for a composite of a 30% decline in eGFR from baseline values or proteinuria > 3.5 g/day according to C3 deposition or the Oxford classification

Variables	All patients		Patients treated with steroid ($n=525$)		Patients not treated with steroid ($n=610$)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.00 (0.99–1.01)	0.00	1.00 (0.99–1.01)	0.645	1.00 (0.99–1.02)	0.392
Sex	1.16 (0.92–1.46)	0.205	1.67 (1.19–2.34)	0.003	0.86 (0.61–1.19)	0.369
M1	0.99 (0.75–1.30)	0.959	1.03 (0.67–1.56)	0.889	0.85 (0.58–1.25)	0.427
E1	1.07 (0.83–1.38)	0.568	1.15 (0.80–1.66)	0.444	1.04 (0.72–1.48)	0.829
S1	0.87 (0.69–1.11)	0.280	0.81 (0.57–1.16)	0.262	0.90 (0.65–1.27)	0.578
T1	1.44 (1.12–1.84)	0.004	1.01 (0.7–1.45)	0.935	1.87 (1.31–2.67)	0.001
T2	2.89 (1.94–4.30)	< 0.001	2.44 (1.23–4.81)	0.01	3.49 (2.07–5.87)	< 0.001
Crescent C1	0.85 (0.58–1.23)	0.396	0.60 (0.29–1.23)	0.165	0.95 (0.61–1.50)	0.854
Crescent C2	0.47 (0.11–1.91)	0.293	NA	0.952	0.79 (0.19–3.29)	0.751
C3 deposition	0.92 (0.73–1.16)	0.498	0.93 (0.66–1.30)	0.686	0.90 (0.66–1.24)	0.546

Data are presented as mean ± SD, median (interquartile range) or *n* (%)

Table 5 Baseline characteristics when nephrotic syndrome patients are excluded

Variables	Total ($n=885$)	C3 deposition		p
		C3 negative ($n=383$)	C3 positive ($n=502$)	
Age (years)	38.95 ± 12.36	38.95 ± 12.41	38.6 ± 12.33	0.720
Male (%)	555 (62.7%)	227	328	0.072
eGFR (ml/min/1.73 m^2)	77.54 ± 40.79	81.47 ± 39.23	74.55 ± 41.72	**0.005**
Proteinuria (mg/day)	2314.01 (2130.88–2497.13)	2421.91 (2064.29–2779.97)	2231.68 (2058.12–2405.24)	0.955
Albumin (g/dL)	3.90 ± 0.60	3.90 ± 0.62	3.90 ± 0.59	0.698
RASi use	538 (60.7%)	240 (62.6%)	298(59.3%)	0.606
Oxford classification				
M1 (%)	542 (79.4%)	221	321	0.593
E1 (%)	176 (25.9%)	65	111	0.169
S1 (%)	386 (56.7%)	137	249	**< 0.001**
T1 (%)	319 (36.4%)	136	183	0.150
T2 (%)	55 (7.8%)	17	38	0.169
Crescent C1 (%)	90 (10.9%)	34	56	0.099
Crescent C2 (%)	13 (1.6%)	9	4	0.150

Statistical significance is set at $p < 0.05$ (in bold)

Data are presented as mean ± SD, median (interquartile range) or n (%)

Table 6 Baseline characteristics when high-risk patients are excluded

Variables	Total ($n=391$)	C3 deposition		p
		C3 negative ($n=175$)	C3 positive ($n=216$)	
Age (year)	36.57 ± 11.88	37.31 ± 11.61	35.98 ± 12.09	0.116
Male (%)	236 (60.4%)	102 (58.3%)	134 (62.0%)	0.468
eGFR (ml/min/1.73 m^2)	103.60 ± 30.2	103.77 ± 28.66	103.46 ± 31.43	0.947
Proteinuria (mg/day)	1030.61 (981.72–1079.50)	1014.87 (937.41–1092.32)	1043.18 (980.17–1106.19)	0.556
Albumin (g/dL)	4.12 ± 0,52	4.09 ± 0,57	4.14 ± 0.47	0.528
RASi use	242 (61.8%)	114 (65.1%)	128 (59.2%)	0.583

Data are presented as mean ± SD, median (interquartile range) or n (%)

mean patient age was lower. In contrast, Wu et al. showed no effect on the prognosis of C3 deposition either in the mesangium or in the glomerular capillaries [11]. The mean patient age and the GFR and proteinuria levels were similar to those in previous studies, but the primary endpoint was a loss of 50% in GFR. In another study in Japan of patients with relatively lower mean GFR and higher 24-h proteinuria, mesangial C3 deposition was observed in 85% of the patients, and no direct effect was detected on prognosis [19].

In the present study, when C3 deposition was evaluated together with the Oxford classification, mesangial C3 deposition in IgAN showed a correlation with the Oxford classification S1 parameter. A similar correlation was not shown with M1, E1, T1-2, and C1-2 lesions. In the multivariate Cox model, the correlation between S1 and C3 deposition was not associated with a significantly increased risk of the primary endpoint. Nasri et al. reported a significant relationship between the C3 deposition score and S and E lesions [10]. In a study by the Korean Glomerulo Nephritis Study (KoGNET) Group, it was concluded that mesangial C3 deposition alone and together with M1, S1, and T1-2 indicated negative renal endpoints [20]. Although the age was similar to that of the present study, proteinuria levels were lower and GFR was higher at the time of diagnosis. In the VALIGA study by Coppo et al., 1147 patients from 13 European countries were examined, encompassing the whole spectrum of IgAN [21]. The independent predictors of each prognosis in the Oxford classification were evaluated. In this study, apart from E1 lesions, M1, S1, and T1-2 lesions were each confirmed as independent predictors of prognosis. It was concluded that endocapillary proliferation was a risk factor for progression in patients with a clinically silent course and a

low level of proteinuria. The correlation found in the current study between S1 lesions and C3 deposition and the absence of correlation with E1 lesions could be attributed to the fact that, compared to other studies, the patient population of this study included more high-risk patients who required steroid or immunosuppressive treatment. The correlation with M1 and T1-2 lesions was not different. As in the VALIGA study, M1 lesions in high-risk patient groups have weak predictive effect for prognosis [22, 23].

In the current study, steroid treatment was found to improve prognosis, especially in patients with T1-2 lesions. No relationship was found between C3 deposition and steroid treatment on prognosis. Reports related to studies, including repeat kidney biopsies, have shown potential healing in certain histological lesions, including mesangial and endocapillary hypercellularity and crescents [24]. In patients with intense IgA deposition treated with steroids, the risk of ESKD has been found to be significantly low [19]. While MST scores have been shown to be strongly related to outcomes in patients not taking steroids or immunosuppressive drugs, this effect was not found in those receiving this treatment [21]. The rate of steroid use was high in the current study, similar to the study by Katafuchi et al., which also showed that mesangial C3 deposition was not related to a poor prognosis [19]. In studies that have shown that mesangial C3 deposition, either alone or together with the Oxford classification, does not indicate a poor prognosis patients receiving steroid treatment were 46% in the current study, 36% in the study by Katafuchi et al., and 20.3% in the study by Wu et al. [11, 19]. In contrast, in studies which stated that C3 deposition is a marker of poor prognosis, < 20% of the patients were treated by steroids [14, 17, 18, 20].

Furthermore, we analysed data according to proteinuria levels. High-risk patients show more compliance with follow-up programs. The biopsy indications are usually proteinuria of > 1 gr/day at the time of diagnosis, proteinuria together with haematuria or an increase in serum creatinine levels. In patients with low-grade proteinuria (protein excretion < 0.5–1 gr/day) accompanied by a high serum creatinine level, when there is no evidence of haematuria or systemic disease (e.g., systemic lupus erythematosus), a biopsy may not be necessary [25].

Interestingly, several studies, together with the current study, show a correlation between C3 deposition and the presence of haematuria. C3 deposition may reflect active disease and the severity of complement activation.

In this study, we report that C3 deposition does not make an additional contribution to the Oxford classification scoring system in high-risk patients in terms of prognosis. It is possible that steroid treatment obscures the effect of C3 deposition as a prognostic marker. However, elevated proteinuria and low GFR at baseline remain reliable leading biomarkers of poor prognosis.

The features that distinguish ours from other studies are its multicentre design, as well as the presence of high-risk patients in the study population. The result that C3 deposition has no effect on prognosis did not change between the analysis of the total patient population and in the subgroup analyses when patients with nephrotic syndrome or other high-risk conditions were excluded. In addition, this is the first study we know to have been conducted in the European area.

There are some limitations to this study. The intrinsic nature of observational, retrospective studies constitutes a first limitation. Another limitation was that there was greater participation in the follow-up programs by patients with higher proteinuria levels or with lower GFR. Despite these limitations, the data of this study are real-life data.

In conclusion, although a correlation was observed between mesangial C3 deposition and the S1 Oxford classification parameter, our data do not support that mesangial C3 be proposed as a prognostic factor in IgAN.

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Data availability The datasets collected and analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors state that there is no conflict of interest.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and approval by the Ethics Committee of Istanbul University Faculty of Medicine (Number: 09/28.06.2011).

Financial interests The authors have no relevant financial or non-financial interests to disclose.

Human and animal rights The present study complies with the guidelines for human studies. This study does not contain any studies with animals.

Informed consent Informed consent was obtained from all subjects involved in the study.

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