International Immunopharmacology 66 (2019) 13–18

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Serum immunoglobulin G provides early risk prediction in immunoglobulin A nephropathy

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ARTICLE INFO

Keywords:
IgA nephropathy
Immunoglobulin G
Prognosis
Risk factors
ESRD

ABSTRACT

Background: Immunoglobulin A (IgA) nephropathy (IgAN) is a common primary glomerular disease that potentially leads to renal failure, risk prediction of declining kidney function is crucial for early clinical management. Immunoglobulin G (IgG) is an important constituent of the immune system and serves as the preferred therapeutic target in human autoimmune diseases. However, its role in the progression of IgAN is unclear.

Methods: From May 2009 to April 2014, 455 patients diagnosed with IgAN at the Second Xiangya Hospital were enrolled in this study; the median follow-up was 42.2 months. All subjects were divided into four groups according to IgG level quartiles. The study endpoint was end-stage renal disease (ESRD) or an irreversible 50% estimated glomerular filtration rate (eGFR) reduction. Clinical data and pathological features of renal biopsy specimens were collected.

Results: Among IgAN patients, serum IgG levels were directly correlated with the levels of serum albumin and serum IgA but reversely correlated with body weight, systolic blood pressure, and serum creatinine and cholesterol levels. According to stratified analysis of serum IgG, the proportions of composite renal endpoints among the enrolled IgAN patients in the serum IgG concentration subgroups 1 (< 7.86), 2 (7.86–10.30), 3 (10.31–12.70), and 4 (> 12.71 g/l) were 9.6%, 9.2%, 3.7%, and 3.7% respectively. Importantly, cumulative renal survival rates were significantly higher in the patients with increased serum IgG ($p = 0.0114$). Serum IgG was also predictive of renal survival, with an HR of 0.745 (95% CI, 0.614 to 0.905, $p = 0.003$) after adjusting for significant factors in the univariate Cox regression and an HR of 0.871 (95% CI, 0.780 to 0.973, $p = 0.014$) adjusting for traditional risk factors of IgAN.

Conclusion: These findings demonstrate that a decreased serum IgG level at the time of renal biopsy is independently associated with a poor renal outcome in IgAN patients.

1. Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is one of the most frequently occurring types of primary glomerulonephritis worldwide and can ultimately lead to end-stage renal disease (ESRD) within 10 to 20 years [1,2]. Since the natural history of IgAN includes conditions ranging from asymptomatic microscopic hematuria or proteinuria to progressive kidney failure, the identification of individuals who are at high risk of future loss of kidney function is crucial [3–5]. Previous studies have reported that proteinuria, hypertension, histological changes in biopsy samples and many other factors can affect renal outcome in patients with IgAN [4,6]. We also previously found some factors that may be associated with the development and progression of IgAN in our center [7–9].

IgAN is regarded as an immune-mediated oligosymptomatic glomerulonephritis caused by the mesangial deposition of circulating immune complexes (CIC) consisting of galactose-deficient IgA1 (Gd-IgA1) bound by autoantibodies [10]. An analysis of CIC in the blood of IgAN patients has revealed that the predominant antibodies are IgG [11,12]. Shin et al. [13] demonstrated that IgAN patients with glomerular IgG deposition have a significantly higher renal progression risk than patients without glomerular IgG deposition; in addition, these authors identified glomerular IgG deposition as a risk factor independent of other variables based on Cox regression analysis. Dong et al. [14] found that serum IgG levels were negatively related to IgG deposition. Compared with the detection of glomerular deposition, the detection of

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https://doi.org/10.1016/j.intimp.2018.10.044
Received 14 July 2018; Received in revised form 30 October 2018; Accepted 31 October 2018
Available online 09 November 2018

serum IgG levels is much easier in the clinic. The current retrospective cohort study was performed to evaluate the predictive value of serum IgG for disease progression in IgAN patients.

2. Methods

2.1. Entry and exclusion criteria

A total of 455 patients with IgAN were identified in a retrospective review of all native renal biopsies performed at the Second Xiangya Hospital of Central South University from May 2009 to April 2014. The inclusion criteria were as follows: (1) a diagnosis of IgAN based on predominant mesangial IgA-containing immune complexes detected by immunofluorescence and light microscopy, (2) a minimum of 5 mm of cortex and 8 glomeruli in the light microscopy sections, and (3) a follow-up time of at least 2 years. Patients with ESRD on admission, combined with other glomerular diseases or with systemic diseases (systemic lupus erythematosus, diabetes mellitus, Henoch-Schönlein purpura, liver cirrhosis, etc.) or patients with incomplete clinical and follow-up data, were excluded based on their clinical history, physical examination, and laboratory test results. The renal endpoint in this study was a composite of ESRD or irreversible 50% estimated glomerular filtration rate (eGFR) reduction. Similar to the methods used in previous studies [15–17], the subjects in this study were divided into 4 groups according to the serum IgG quartiles.

All methods used in this study were approved by the Ethics Committee of the Second Xiangya Hospital, Central South University, and we obtained informed consent from all patients before conducting the study.

2.2. Clinical and laboratory data collection

The clinical and laboratory data of all 455 patients included in our study were collected. The parameters included sex, age, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), related blood biochemical indices, and urinalysis data. Twenty-four-hour urine samples were collected for the determination of urine protein excretion. Hypertension was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg. Anemia was defined as hemoglobin < 110 g/l in females and < 120 g/l in males. eGFR was evaluated with the modified Modification of Diet in Renal Disease (MDRD) equation [18]. All laboratory data were evaluated the day before renal biopsy.

2.3. Renal pathology evaluation

Renal biopsies were scored according to the MEST-C scoring system, proposed by the IgA Nephropathy Classification Working Group [19]. At least two pathologists blinded to patient outcomes at the time of review confirmed the pathological results [20]. The histologic classification was performed as follows: M0 indicated a mesangial score ≤ 0.5, or ≤ 50% of glomeruli with ≥ 4 mesangial cells per mesangial area; M1 indicated a mesangial score > 0.5, or > 50% of glomeruli with ≥ 4 mesangial cells per mesangial area; E0 or E1 indicated the presence or absence of endocapillary hypercellularity, respectively; S0 or S1 indicated the presence or absence of segmental sclerosis or tuft adhesions, respectively, and T0, T1, and T2 indicated the degree of tubular atrophy or interstitial fibrosis (< 25%, 25–50%, and > 50%, respectively). C0, C1, and C2 indicated no crescent in glomeruli, crescent in < 25% of glomeruli, and crescent in > 25% of glomeruli, respectively.

2.4. Statistical analysis

SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables are expressed as the means ± SD, and the grouped data are expressed as percentages where appropriate. Chi-square tests were used to analyze the categorical variables and continuous variables were compared by using a one-way ANOVA. Cumulative survival was estimated with Kaplan-Meier survival curves and analyzed by using the log-rank test. A Cox proportional hazard regression model was used to assess the association between the baseline variables and the clinical outcomes. Here, we used the coefficient (B), hazard ratio, HR (HR = EXP (B)), and the 95% confidence interval (95% CI) to reflect changes in the dependent variable in response to single-unit changes in the independent variable. To identify independent predictors of progression, we performed a multivariate Cox regression analysis with a selection of variables. p values < 0.05 were considered statistically significant.

3. Results

3.1. Participants

From December 2009 to January 2014, a total of 648 IgAN patients were recorded in the database, including 7 patients with an eGFR < 15 ml/min/1.73 m^2 at the time of biopsy; 21 patients with additional systemic diseases, such as systemic lupus erythematosus, diabetes mellitus, Henoch-Schönlein purpura and liver cirrhosis and 43 patients without serum IgG data. The remaining 577 IgAN patients were followed for a median of 42.2 months, but 122 of these patients were lost to follow-up (Fig. 1). Hence, 455 patients were enrolled in our cohort. A 50% decline in eGFR was observed in 3.08% (n = 14) of the patients, and 3.08% (n = 14) of the patients developed ESRD during the follow-up period.

3.2. Clinical findings at the time of renal biopsy

The 455 IgAN patients (male 44.4% (n = 202), female 55.6% (n = 253)) in our study were divided into the following 4 groups on the basis of serum IgG quartiles: < 7.86, 7.86–10.30, 10.31–12.70, and > 12.71 g/l. Table 1 shows the clinical characteristics at the time of renal biopsy. Interestingly, there was a marked increase in the percentage of females (p = 0.001) and a decrease in body weight (p = 0.040), SBP (p = 0.003; mean 125.55 ± 16.12 mm Hg) and percentage of hypertension (p = 0.00; mean 24%) with increasing serum IgG. The mean age of all patients was 32.03 ± 11.87 years, the mean DBP was 79.70 ± 12.26 mm Hg, the mean hemoglobin concentration was 130.72 ± 18.39 g/l, and the mean complement 3 (C3) and complement 4 (C4) concentrations were 1.01 ± 0.28 g/l and 0.24 ± 0.13 g/l, respectively. Although there were no significant differences among the

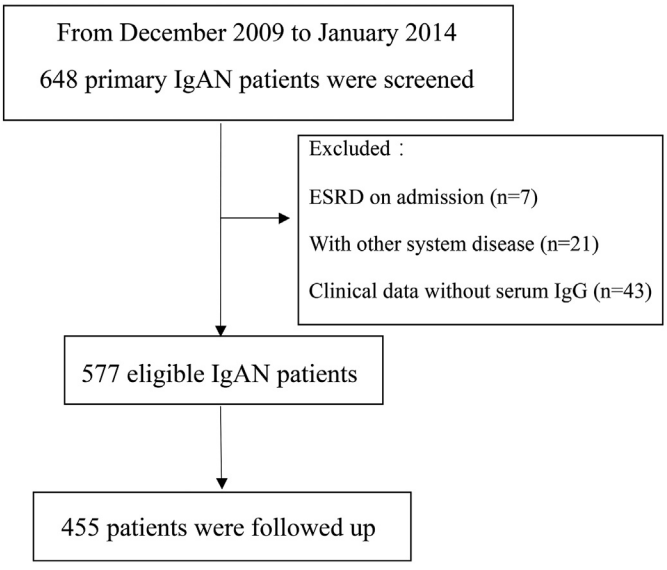

Fig. 1. Derivation of the cohort. Abbreviations: ESRD, end-stage renal disease.

Table 1
Baseline patient characteristics grouped by serum IgG level quartiles.

Variables	All n = 455	Serum IgG (g/l)			
		< 7.86 Group 1 n = 114	7.86–10.30 Group 2 n = 120	10.31–12.70 Group 3 n = 110	> 12.71 Group 4 n = 111
Gender					
Male, %	44.4	51.8	54.2	39.1	31.5*,#
Female, %	55.6	48.2	45.8	60.9	68.5*,#
Age, years	32.03 ± 11.87	32.18 ± 14.75	31.55 ± 11.57	32.32 ± 10.89	32.09 ± 9.77
Weight, kg	59.05 ± 11.02	61.38 ± 11.4	59.20 ± 10.85	58.06 ± 10.98*	57.47 ± 10.55*
SBP, mm Hg	125.55 ± 16.12	129.37 ± 18.10	126.98 ± 16.64	123.34 ± 15.50*	122.29 ± 12.86*,#
DBP, mm Hg	79.70 ± 12.26	81.85 ± 11.94	80.31 ± 12.74	78.71 ± 12.73	77.83 ± 11.31
Hypertension, %	24.0	36.0	25.0	20.9*	13.5*,#
Hemoglobin, g/l	130.72 ± 18.39	134.59 ± 21.12	128.19 ± 16.88	132.32 ± 15.50	127.58 ± 19.05
Anemia, %	16.7	18.8	19.3	10.4	18.3
Serum albumin, g/l	35.74 ± 99.44	24.78 ± 10.51*	38.03 ± 6.17*	39.51 ± 4.78*	40.64 ± 7.49*,#
eGFR, ml/min/1.73 m^2	90.65 ± 32.53	86.09 ± 38.29	89.44 ± 34.09	93.40 ± 26.48	93.91 ± 29.44
Scr (μmol/l)	89.40 ± 42.72	105.65 ± 57.05	93.08 ± 40.71*	80.37 ± 33.21*,#	77.67 ± 28.16*,#
BUN (mmol/l)	5.84 ± 2.97	8.06 ± 4.34	5.56 ± 2.15*	5.03 ± 1.56*	5.06 ± 1.79*
UA (g/l)	347.81 ± 110.01	383.53 ± 104.06	357.53 ± 120.55	320.88 ± 107.44	327.69 ± 95.31
TG (mmol/l)	1.95 ± 1.96	2.68 ± 2.20	2.01 ± 2.43	1.53 ± 1.25	1.55 ± 1.42
CHOL (mmol/l)	5.68 ± 2.99	8.64 ± 4.41	4.92 ± 1.40	4.63 ± 1.02	4.42 ± 0.87
Serum IgA (g/l)	2.53 ± 1.34	2.13 ± 1.22	2.39 ± 1.07	2.71 ± 1.04*,#	2.91 ± 1.08*,#
Serum IgM (g/l)	1.44 ± 0.71	1.57 ± 0.88	1.28 ± 0.60*	1.38 ± 0.60*	1.55 ± 0.68*,#
C3 (g/l)	1.01 ± 0.28	1.05 ± 0.31	1.04 ± 0.31	0.97 ± 0.22	0.98 ± 0.25
C4 (g/l)	0.24 ± 0.13	0.27 ± 0.16	0.24 ± 0.15	0.23 ± 0.77	0.24 ± 0.1
24-hour urinary protein (g)	1.56 ± 2.42	3.60 ± 3.39	1.24 ± 1.80*	0.73 ± 1.29*	0.50 ± 0.53*
Hematuria, %					
−	34.6	43.9	31.8	35.0	28.3
+	30.2	24.5	31.8	30.1	34.3
++	22.1	23.5	18.7	22.3	24.2
+++	13.0	8.2	17.8	12.6	13.1
M					
0	93	90.4	95.8	92.7	92.8
1	7	9.6	4.2	7.3	7.2
E					
0	89.2	90.4	87.5	92.7	85.5
1	10.8	9.6	12.5	7.3	13.5
S					
0	38.2	45.6	30.0	35.5	42.3
1	61.8	54.4	70.0	64.5	57.7
T					
0	65.1	68.4	59.2	68.2	64.9
1	28.8	22.8	34.2	27.3	30.6
2	6.2	8.8	6.7	4.5	4.5
C					
0	77.8	76.3	78.3	77.3	79.3
1	18.7	15.8	19.2	21.8	18.0
2	3.5	7.9	2.5	0.9	2.7

Abbreviations: Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; CHOL, cholesterol; Ig, immunoglobulin; C3, complement 3; C4, complement 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
Differences among quartile subgroups were compared with a chi-squared test for categorical variables and one-way ANOVA for continuous variables.
No difference between group3 and group4.
* $p < 0.05$ vs group 1.
# $p < 0.05$ vs group 2.

four groups in the indices described above, there was a tendency of a decrease in DBP from group 1 to group 4. eGFR also did not show significant differences among groups, but it demonstrated a trend opposite that of serum IgG. The mean values of the renal function indicators, serum creatinine (Scr), blood urea nitrogen (BUN), and uric acid (UA) were 89.40 ± 42.72 μmol/l, 5.84 ± 2.97, and 347.81 mmol/l, respectively. These indicators, as well as triglyceride (TG) and cholesterol (CHOL), showed significant differences among the four groups, but only Scr and CHOL had an evident tendency to decrease from group 1 to group 4. Serum IgA had the same tendency as that of serum IgG, while proteinuria declined with increasing serum IgG ($p < 0.001$). Hematuria and pathology changes according to the Oxford Classification had no obvious regularity.

3.3. Cumulative renal survival rates in IgAN patients

The 1-, 3- and 5-year cumulative renal survival rates of all patients in our cohort were 99.51%, 95.67% and 88.90%, respectively (Fig. 2a), and 9.6%, 9.2%, 3.7%, and 3.7% of the patients in the serum IgG concentration subgroups 1, 2,3 and 4, respectively, reached the composite renal endpoints. The 3-year cumulative renal survival rates in subgroups 1, 2, 3 and 4 were 91.57%, 92.80%, 98.80% and 98.89%, respectively. Kaplan-Meier analysis showed that the cumulative renal survival rates were significantly higher in patients with elevated serum IgG concentrations than the patients with lower IgG concentrations ($p = 0.0114$) (Fig. 2b), were significantly higher in the patients with proteinuria than the patients without proteinuria ($p = 0.0215$) (Fig. 2c), and were significantly higher in the patients with hypertension than the patients without hypertension ($p = 0.0002$) (Fig. 2d).

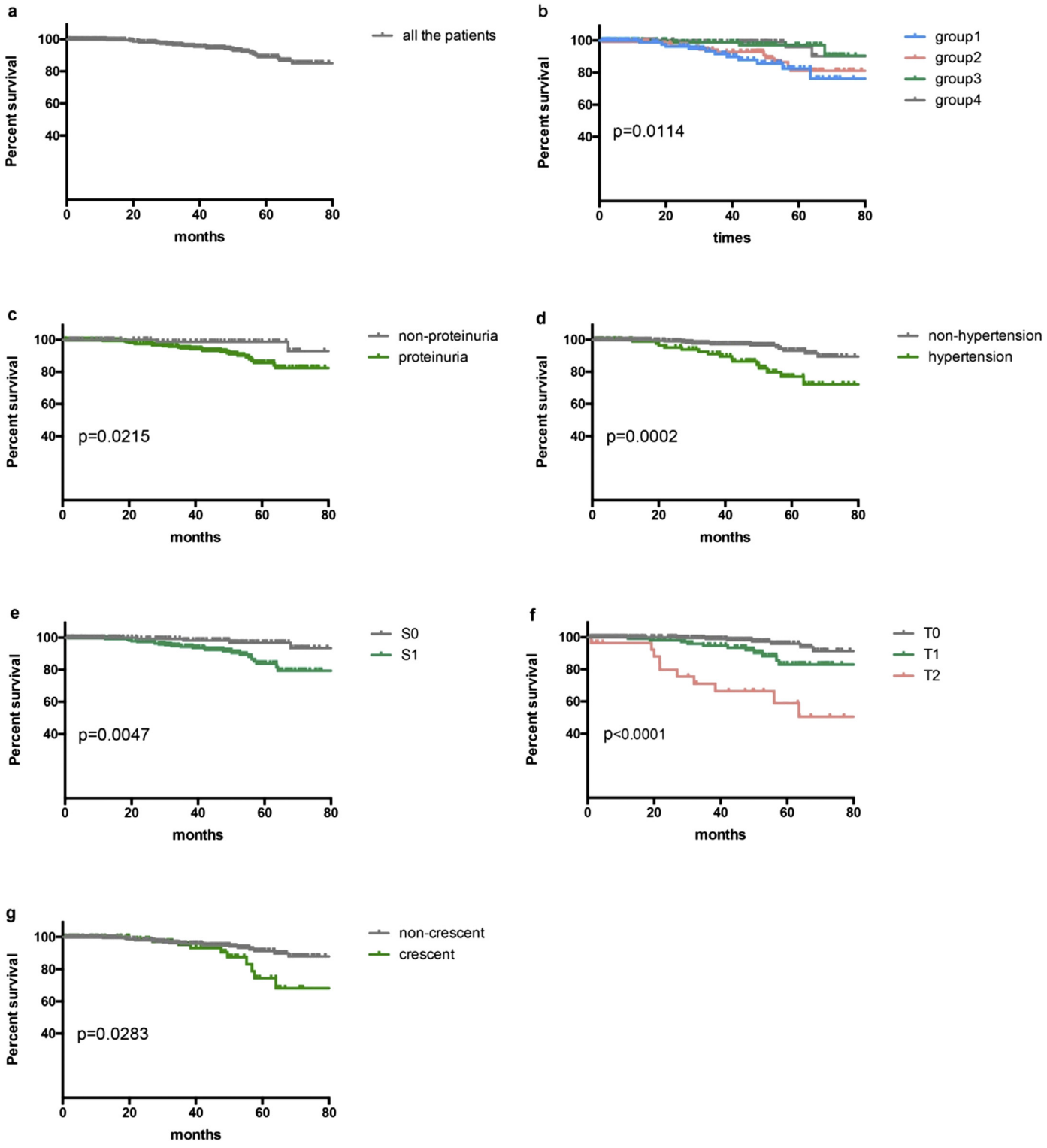

Fig. 2. Kaplan-Meier survival analysis according to different factors.
Cumulative survival was estimated with Kaplan–Meier survival curves, and was analyzed by using the log-rank test.

Kaplan-Meier analysis also showed that different pathological changes according to the MEST-C scores in the Oxford Classification were related to different renal survival rates. Renal survival rates were higher in the patients with S0 than the patients with S1 ($p = 0.0047$) (Fig. 2e), were higher in the patients with T0 than the patients with T1 or T2 ($p < 0.0001$) (Fig. 2f), and were higher in the patients without crescents than the patients with crescents ($p = 0.0283$) (Fig. 2g). No significant differences were observed between E0 and E1.

3.4. Univariate and multivariate analysis of factors associated with renal outcomes

The Cox proportional hazard regression analysis results are shown in Table 2. Univariate analysis (Model 1) revealed that the patients who

Table 2
Univariate and multivariate Cox proportional hazard analyses of the risk of ESRD or a 50% decrease in the eGFR.

Variables	Model 1		Model 2		Model 3	
	HR (95%)	p	HR (95%)	p	HR (95%)	p
Age	1.007 (0.977–1.038)	0.633				
Gender (female)	0.709 (0.327–1.536)	0.383				
SBP	1.025 (1.006–1.044)	0.010	0.993 (0.954–1.033)	0.720	1 (0.965–1.037)	0.987
DBP	1.037 (1.009–1.065)	0.009	1.013 (0.959–1.070)	0.648	1.004 (0.9702–1.038)	0.797
Hemoglobin	0.959 (0.936–0.982)	0.001	0.963 (0.932–0.995)	0.023		
Serum albumin	0.963 (0.929–0.997)	0.035	1.067 (0.991–1.149)	0.087		
Scr	1.021 (1.016–1.026)	< 0.001	1.007 (0.996–1.018)	0.203		
BUN	1.188 (1.104–1.279)	< 0.001	1.075 (0.830–1.393)	0.583		
UA	1.006 (1.003–1.010)	< 0.001	0.996 (0.991–1.002)	0.176		
TG	1.046 (0.888–1.232)	0.593				
CHOL	1.020 (0.888–1.173)	0.777				
Serum IgA	1.001 (0.717–1.399)	0.994				
Serum IgG	0.860 (0.779–0.950)	0.003	0.745 (0.614–0.905)	0.004	0.871 (0.780–0.973)	0.014
Serum IgM	0.430 (0.215–0.862)	0.017	0.477 (0.224–1.014)	0.054		
Serum C3	1.447 (0.399–5.251)	0.575				
Serum C4	9.526 (2.713–33.375)	< 0.001	7.731 (0.208–287.112)	0.267		
eGFR	0.957 (0.942–0.972)	< 0.001	0.960 (0.939–0.982)	< 0.001	0.871 (0.780–0.973)	0.004
24-hour urinary protein	1.153 (1.038–1.282)	0.008	0.898 (0.648–1.243)	0.516	0.920 (0.813–1.210)	0.938
Oxford Classification: M0	1 (reference)					
Oxford Classification: M1	0.45 (0.000–30.317)	0.350				
Oxford Classification: E0	1 (reference)					
Oxford Classification: E1	0.616 (0.146–2.596)	0.509				
Oxford Classification: S0	1 (reference)		1 (reference)		1 (reference)	
Oxford Classification: S1	4.104 (1.420–11.860)	0.009	0.580 (0.150–2.239)	0.429	1.473 (0.460–4.721)	0.514
Oxford Classification: T0	1 (reference)		1 (reference)		1 (reference)	
Oxford Classification: T1	3.272 (1.268–8.443)	0.014	2.368 (0.548–10.227)	0.248	1.896 (0.679–5.297)	0.222
Oxford Classification: T2	13.714 (5.214–36.069)	< 0.001	3.442 (0.662–17.894)	0.142	4.920 (1.616–14.976)	0.005
Oxford Classification: C0	1 (reference)		1 (reference)		1 (reference)	
Oxford Classification: C1	2.409 (1.110–5.227)	0.026	1.443 (0.423–4.850)	0.563	2.322 (0.989–5.451)	0.053
Oxford Classification: C2	4.104 (1.420–11.860)	0.009	1.460 (0.099–21.434)	0.783	1.831 (0.389–8.614)	0.444

Model 1 is a univariate analysis model. Model 2 is adjusted for the following clinical parameters: SBP, DBP, hemoglobin, serum albumin, Scr, BUN, UA serum IgG, serum IgM, serum C4, eGFR, 24-hour urinary protein, S scores in Oxford Classification, T scores in Oxford Classification and C scores. Model 3 is adjusted for the following clinical parameters: SBP; DBP; serum IgG; eGFR; 24-hour urinary protein; and S, T and C scores in the Oxford Classification.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure. Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; CHOL, cholesterol; Ig, immunoglobulin; C3, complement 3; C4, complement 4. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
The Cox proportional hazard regression model was used to assess the association between the baseline variables and the clinical outcomes.

had lower levels of serum IgG, higher levels of SBP, DBP, Scr, BUN, UA, and proteinuria, more serious interstitial fibrosis and tubular atrophy, and crescents were at a greater risk of poor renal outcomes. Multivariate Cox (Model 2) regression analysis was adjusted for the significant factors in Model 1 and showed that each increase in eGFR (by 1 ml/min/1.73 m^2), serum IgG (by 1 g/l), and hemoglobin (by 1 g/l) was predictive of renal survival rates with HRs of 0.960 (95% CI: 0.939 to 0.982, $p < 0.0001$), 0.745 (95% CI: 0.614 to 0.905, $p = 0.003$), and 0.963 (95% CI, 0.932 to 0.995, $p = 0.023$), respectively, indicating that these variables served as independent predictors of unfavorable outcomes. In another multivariate model after adjusting for traditional independent risk factors (Model 3), an increase in IgG (by 1 g/l) was also related to the development of the outcomes (HR: 0.871, 95% CI: 0.780 to 0.973, $p = 0.014$).

4. Discussion

Dozens of factors have been found to be related to the renal outcome in IgAN patients in recent decades, including eGFR, proteinuria, and blood pressure [4,6,21,22]. In IgAN patients, IgG anti-Gd-IgA1 antibodies and soluble CD89 (Fc α receptor), which are components of CIC, may serve as candidate diagnostic markers for predicting the risk of disease progression and reflect prominent defects in mucosal immunity [23]. Regarding to histological changes, glomerular IgG deposition was also associated with disease progression. Patients with glomerular IgG deposition have poorer renal outcomes [13,24–26]. Dong et al. [14] showed that serum IgG levels decreased as pathological IgG grade increased in IgAN patients and proved that glomerular IgG deposition might not be derived from CICs. In addition, severe infections and toxicity after renal transplantation are associated with significant reductions in serum IgG [27]. IgG is the most common subtype of immunoglobulins, which protect against disease to a considerable extent by activating complement, aggregating microbial pathogens, and interacting with IgFc receptors (FcRs) [28,29]. Renal function in IgAN patients is associated with complement dysregulation and low Fc α receptor levels [30].

In this analysis, IgAN patients were divided into 4 groups according to the quartiles of the serum IgG levels. As shown in Table 1, higher IgG levels were associated with lower SBP, Scr, UA, and CHOL levels, proteinuria, and more severe pathological changes. However, there were no differences in hematuria or pathological changes among the groups. Thus, patients with lower levels of serum IgG were at higher risk of disease progression. Kaplan–Meier analysis also showed the same result. As shown in Fig. 2b, patients with lower IgG levels had a lower survival rate in terms of composite renal endpoints. Our data showed that IgG played an independent predictive role after adjusting for the significant factors in univariate analysis (HR = 0.745, 95% CI: 0.614–0.905, $p = 0.003$) and after adjusting for traditional clinical risk factors (HR = 0.871, 95% CI 0.780–0.973, $p = 0.014$). The M scores were excluded from the Oxford MEST-C scores (none of 32 patients with M1 exhibited the endpoints, thus, the M scores could not be analyzed). Although previous studies have reported that crescents predict a higher risk of poor renal outcome, different criteria were used in those studies [31,32]. We used the criteria of C0 (no crescents), C1 (crescents in more than zero but less than one-fourth of glomeruli) and C2 (crescents in one-fourth or more of glomeruli) in our analysis

according to the update by the IgA Nephropathy Classification Working Group [19].

Berthoux et al. [33] reported that IgG was a biomarker for the prediction of 34 clinicopathologic recurrence events (HR = 1.08, 95% CI: 1.00–1.16, p = 0.05), but renal survival was not discussed in that study. Strait et al. [34] showed that IgG1-deficient mice developed early renal disease and suggested that poorly activate effector mechanisms of IgG isotypes may be useful for inhibiting IC immunopathology. There have been no similar studies investigating IgAN, and further research is needed to determine whether the IgG subclass plays a key role in IgAN.

Although the current study demonstrated the predictive role of serum IgG in IgAN patients, several limitations need to be noted. First, several patients were lost to follow-up, and a few patients lacked serum IgG data, resulting in selection bias. Second, unadjusted confounding from the unified treatment regimens impaired the stringency of our data. Third, although we initially excluded patients with other systemic diseases from our study, serum IgG is a nonspecific immunoglobulin that might be affected by other complicating factors that could confound the results. Fourth, the influence of serum IgG should be further evaluated by long-term multicenter studies.

In conclusion, in adult patients with IgAN, a decrease in serum IgG level at the time of renal biopsy is independently associated with unfavorable renal outcomes, even after adjusting for other significant univariate factors, traditional clinical risk factors and Oxford pathological parameters. Further studies are needed to confirm our results.

Conflict of interest

The authors have no conflicts of interest to disclose. All other authors have read the manuscript and have agreed to submit it in its current form for consideration for publication in the journal.

Acknowledgments

This work was supported by a research grant (81470947 and 81770714) from the National Natural Science Foundation of China.

Declaration of interest

The authors have no conflicts of interest to declare. The authors alone are responsible for the content of this manuscript.

Author contributions

Conceived and designed the experiments: Hong Liu and Di Liu. Performed the experiments: Di Liu, Jing You, Yexin Liu, Xiaofang Tang, Xia Tan, Fan Zhang. Analyzed the data: Di Liu, Ming Xia, Lingzhi Wu, Guochun Chen, Liyu He, Xuejing Zhu. Wrote the paper: Di Liu.

References

[1] R.J. Wyatt, B.A. Julian, IgA nephropathy, N. Engl. J. Med. 368 (25) (2013) 2402–2414.
[2] W. Le, et al., Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population, Nephrol. Dial. Transplant. 27 (4) (2012) 1479–1485.
[3] J. Floege, K. Amann, Primary glomerulonephritides, Lancet 387 (10032) (2016) 2036–2048.
[4] S.J. Barbour, H.N. Reich, Risk stratification of patients with IgA nephropathy, Am. J. Kidney Dis. 59 (6) (2012) 865–873.
[5] H. Liu, et al., Renal biopsy findings of patients presenting with isolated hematuria: disease associations, Am. J. Nephrol. 36 (4) (2012) 377–385.
[6] F. Berthoux, et al., Predicting the risk for dialysis or death in IgA nephropathy, J. Am. Soc. Nephrol. 22 (4) (2011) 752–761.
[7] W.L. Jiang, et al., Evaluation of renal clinicopathological changes in IgA nephropathy by urinary podocytes excretion and podocalyxin expression, Ren. Fail. 34 (7) (2012) 821–826.
[8] W. Li, et al., TLR9 and BAFF: their expression in patients with IgA nephropathy, Mol. Med. Rep. 10 (3) (2014) 1469–1474.
[9] G. Wu, et al., The role of memory B cell in tonsil and peripheral blood in the clinical progression of IgA nephropathy, Hum. Immunol. 74 (6) (2013) 708–712.
[10] J. Novak, et al., New insights into the pathogenesis of IgA nephropathy, Kidney Dis. (Basel) 1 (1) (2015) 8–18.
[11] M. Tomana, et al., Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies, J. Clin. Invest. 104 (1) (1999) 73–81.
[12] H. Suzuki, et al., Aberrantly glycosylated IgA1 in IgA nephropathy patients is recognized by IgG antibodies with restricted heterogeneity, J. Clin. Invest. 119 (6) (2009) 1668–1677.
[13] D.H. Shin, et al., Glomerular IgG deposition predicts renal outcome in patients with IgA nephropathy, Mod. Pathol. 29 (7) (2016) 743–752.
[14] J. Dong, et al., A pilot and comparative study between pathological and serological levels of immunoglobulin and complement among three kinds of primary glomerulonephritis, BMC Immunol. 19 (1) (2018) 18.
[15] T. Isakova, et al., Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease, JAMA 305 (23) (2011) 2432–2439.
[16] S. Araki, et al., Urinary potassium excretion and renal and cardiovascular complications in patients with type 2 diabetes and normal renal function, Clin. J. Am. Soc. Nephrol. 10 (12) (2015) 2152–2158.
[17] P.S. Garimella, et al., Association of serum erythropoietin with cardiovascular events, kidney function decline, and mortality: the Health Aging and Body Composition Study, Circ. Heart Fail. 9 (1) (2016) e002124.
[18] Y.C. Ma, et al., Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease, J. Am. Soc. Nephrol. 17 (10) (2006) 2937–2944.
[19] H. Trimarchi, et al., Oxford classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group, Kidney Int. 91 (5) (2017) 1014–1021.
[20] X. Zhu, et al., Tubular atrophy/interstitial fibrosis scores of Oxford classification combinded with proteinuria level at biopsy provides earlier risk prediction in lgA nephropathy, Sci. Rep. 7 (1) (2017) 1100.
[21] S.J. Barbour, et al., The MEST score provides earlier risk prediction in lgA nephropathy, Kidney Int. 89 (1) (2016) 167–175.
[22] Y. Liu, et al., Risk factors for pregnancy outcomes in patients with IgA nephropathy: a matched cohort study, Am. J. Kidney Dis. 64 (5) (2014) 730–736.
[23] T. Robert, et al., Molecular insights into the pathogenesis of IgA nephropathy, Trends Mol. Med. 21 (12) (2015) 762–775.
[24] S.S. Bellur, et al., Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford classification patient cohort, Nephrol. Dial. Transplant. 26 (8) (2011) 2533–2536.
[25] M.G. van Dixhoorn, et al., Combined glomerular deposition of polymeric rat IgA and IgG aggravates renal inflammation, Kidney Int. 58 (1) (2000) 90–99.
[26] Y. Wada, et al., Clinical significance of IgG deposition in the glomerular mesangial area in patients with IgA nephropathy, Clin. Exp. Nephrol. 17 (1) (2013) 73–82.
[27] G. Ku, et al., Serum IgG and renal transplantation, Br. Med. J. 4 (5894) (1973) 702–707.
[28] F. Nimmerjahn, J.V. Ravetch, Fcgamma receptors as regulators of immune responses, Nat. Rev. Immunol. 8 (1) (2008) 34–47.
[29] R. Barrington, et al., The role of complement in inflammation and adaptive immunity, Immunol. Rev. 180 (2001) 5–15.
[30] J. Mestecky, et al., IgA nephropathy: molecular mechanisms of the disease, Annu. Rev. Pathol. 8 (2013) 217–240.
[31] W. Zhang, et al., Clinical outcomes of IgA nephropathy patients with different proportions of crescents, Medicine (Baltimore) 96 (11) (2017) e6190.
[32] M. Haas, et al., A multicenter study of the predictive value of crescents in IgA nephropathy, J. Am. Soc. Nephrol. 28 (2) (2017) 691–701.
[33] F. Berthoux, et al., Prognostic value of serum biomarkers of autoimmunity for recurrence of IgA nephropathy after kidney transplantation, J. Am. Soc. Nephrol. 28 (6) (2017) 1943–1950.
[34] R.T. Strait, et al., IgG1 protects against renal disease in a mouse model of cryoglobulinaemia, Nature 517 (7535) (2015) 501–504.