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Association Between Serum IgG Concentrations and Prognosis in IgA Nephropathy

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Original Paper

Introduction. To investigate the relationship between serum IgG (sIgG) concentration and the prognosis of IgA nephropathy (IgAN).
Methods. A total of 309 patients with biopsy-proven IgAN in the Second Referral Hospital of Shenzhen were enrolled between 2010/01 and 2017/06. Patients were divided into 3 groups on the basis of sIgG tertiles: < 8.99 g/L (Group G1), 8.99 to 11.17 g/L (Group G2), and > 11.17 g/L (Group G3).
Results. As the level of sIgG increased, there was a decrease in DBP, serum creatinine, 24h urine proteinuria and an increase in serum albumin (all $P < .05$). In terms of pathological manifestations, with increasing sIgG levels, there was a tendency of decline in the Lee's grading system or high-grade tubular atrophy/interstitial fibrosis or in the proportion of glomerular sclerosis and the ratio of crescent (all $P < .05$). Kaplan-Meier analysis indicated that the cumulative renal survivals rates were significantly higher in patients with elevated sIgG ($P < .05$). Cox regression analysis showed that after adjusting for gender, age, BMI, and clinical indicators (BP, 24h urine proteinuria, eGFR, M, E, S, T, and the ratio of crescent), decreased sIgG level at the time of renal biopsy is an independent risk factor for unfavorable outcomes in IgAN. Furthmore, every 1 g/L decrease in sIgG level was associated with a 1.74-fold (95% CI: 1.30 to 5.38) increased risk of the incidence of composite renal outcomes.
Conclusions. Decreased serum IgG level at baseline might be a kind of predictive marker for the poor prognosis of IgAN.

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INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in China and even around the world,[1] and is one of the main causes of end-stage renal disease (ESRD).[2] The pathogenesis of IgAN is still unclear and is considered to be related to autoimmune abnormalities; the most recognized pathogenesis is the multiple percussion theory:[3-5] The IgA molecules with O-glycosylation abnormalities (Galactose-deficient IgA1, Gd-IgA1) produced by the B cells in patients with IgAN may cause the first strike, which may combine the second strike caused by specific antibodies and form the circulating IgAl immune complex to caused the third strike; later, the deposition of such complex in glomerular mesangial area stimulates the immune inflammatory response and in turn causes kidney damages (the fourth strike), thus promoting the occurrence and progression of diseases.[4] Previous studies have shown that[6-8] the antibodies to the immune complex in IgAN are mainly the IgG antibodies. Dong *et al.*[9] has revealed a negative correlation between the sIgG level and renal IgG deposition intensity in IgAN patients. In addition, Liu *et al.*[10] reveals that low sIgG levels may herald an adverse prognosis in IgAN patients. These

studies have suggested that the sIgG concentration may be associated with the clinical severity and prognosis in patients with IgAN, but the sample sizes in former studies were relatively small and the relationship between sIgG concentration and patients' prognosis was not fully investigated, and the value of sIgG on the renal outcomes of IgAN was not further quantified. Therefore, in order to further study the association of sIgG concentration with the prognosis of patients with IgAN. This study analyzed the clinical pathology and follow-up data of patients and explored the relationship between sIgG concentration and prognosis of IgAN in order to assist physicians in predicting renal outcomes for IgAN patients and providing effective treatments.

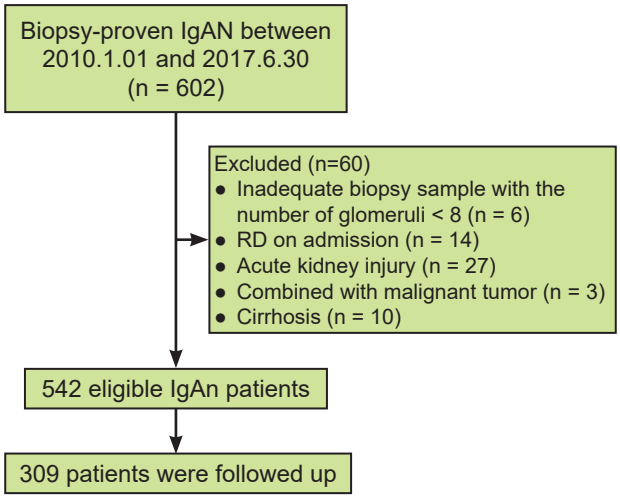

Figure 1. Flow Diagram of the Study

MATERIALS AND METHODS

Patients

This study was a single-center, retrospective cohort . From January 1,2010 to June 30, 2017, 602 cases were diagnosed as IgAN via renal biopsy in the Second Referral Hospital of Shenzhen. The exclusion criteria included: (1) fewer than eight glomeruli in a renal tissue section for diagnosis; (2) secondary IgA deposition caused by purpura, chronic hepatitis, systemic lupus erythematous, and others; (3) incidence of malignant tumor, acute severe infection and acute kidney injury;(4) renal transplant recipients; (5) age < 14 years. Patients with a follow-up time of more than 1 year were enrolled. Hence, 309 patients were enrolled in our study. The flowchart of study is summarized in Figure 1. Our study has been conducted in accordance with the declaration of Helsinki; informed consent has been obtained from the participants. The study was approved by the Ethics Committee of Shenzhen Second Peopls's Hospital.

Clinical Data

The demographic data and general clinical data of the patients, including the age, sex, body mass index (BMI), and blood pressure were collected. Laboratory indicators such as hemoglobin, serum creatinine, blood uric acid, total protein, albumin, 24h proteinuria, serum IgA, serum IgM, serum IgG, serum complement C3/C4 etc were obtained from the patients' records. All laboratory data were evaluated the day before renal biopsy. Serum concentrations of immunoglobulins (Igs) A or G or M or C4 and C3 were measured by immunoturbidimetry (Cobas C501, Roche, Mannhein, Germany). eGFR was calculated by using the modified Modification of Diet in Renal Disease (MDRD) equation.[11] Therapeutic regimens were collected in each group, including information on the use of renin-angiotensin system inhibitors (RASi), corticosteroids and immunosuppressant.

Pathological Data

The renal biopsy tissue was embedded in paraffin, followed by 2 to 3 mm serial slicing, conventional HE, periodic acid Schiff (PAS), hexammonium iodate silver horseshoe (PASM), and Masson staining. Immunohistochemistry was performed to detect the expression intensities and deposition sites of IgA, IgM and complement C3 by direct immunofluorescence. Histological specimens were evaluated by Kingmed Diagnostics center using the Lee's Grade[12] and Oxford classification.[13] In Grade I IgA nephropathy, the glomeruli are histologically normal without crescents/segmental lesions (sclerosis, adhesions, necrosis). In Grade II IgA nephropathy, < 50% of the glomeruli show proliferation of mesangial cells, with or without crescents/segmental lesions in < 15% glomeruli. In Grade III IgA nephropathy, > 50% of the glomeruli show proliferation of mesangial cells, with crescents/segmental lesions in < 50% glomeruli. In Grade IV IgA nephropathy, was like Grade III but with crescents/segmental lesions/total glomerular sclerosis in 50 to 75% glomeruli. In Grade V IgA nephropathy, was like Grade

III but with crescents/segmental lesions/total glomerular sclerosis in > 75% glomeruli. The Oxford 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 hyper cellularity, 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 to 50%, and > 50%; respectively). The ratio of glomerular sclerosis referred to the proportion of glomerular sclerosis in the total number of glomeruli. The proportion of the crescent referred to the proportion of glomeruli with formed crescent to the total number of glomeruli.

Study Outcomes

The composite endpoint was defined as 30% decline of eGFR from baseline or occurrence of ESRD. ESRD was defined as eGFR < 15 mL/min/1.73m^2 or initiation of renal replacement therapy including permanent hemodialysis, peritoneal dialysis, or renal transplantation.

Statistical Methods

The normally distributed measurement data were expressed as mean ± SD, otherwise median and interquartile range (IQR) plus 25 to 75th percentiles. To test for difference in categorical or continuous variables among group, chi-squared test, Mann–Whitney test, or Kruskal–Wallis test were used. The count data were expressed by ratio or composition ratio, and the intergroup comparison used the x^2 test. The correlation analysis of normally distributed data was analyzed by the Pearson method, otherwise the Spearman method. To identify the independent risk factors, we performed univariate Cox regression models. When *P* value is less than .05, the variables will beincluded in multivariable Cox regression models using the 'Forward' method. Hazard ratios (HR) and 95% confidence intervals (CI) were provided. The impact of sIgG level on the renal endpoint events of IgAN was quantified by multivariate Cox proportional model. The Kaplan-Meier survival curve analysis was used to compare the prognostic differences among groups with different sIgG levels. All analyses were performed with Empower Stats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA), and statistical significance was defined as $P < .05$.

RESULTS

Baseline Clinical Data

Table 1 shows the baseline clinical data of the 309 patients. The mean age was (35.34 ± 9.19) years, and 154 (49.8%) were male. According to the tertiles sIgG value, the patients were divided

Table 1. Baseline Clinical Data of 309 IgAN Patients

Variable	Sum (n = 309)	Serum IgG (g/L)			*P*
		G1 (< 8.99, n = 102)	G2 (8.99 to 11.17, n = 103)	G3 (> 11.17, n = 104)	
Male [n, (%)]	154 (49.84)	59 (57.84)	49 (47.57)	46 (44.23)	> .05
Age	35.34 ± 9.19	33.44 ± 7.10	35.88 ± 9.74	35.93 ± 9.43	> .05
BMI, kg/m^2	23.11 ± 3.32	22.82 ± 3.27	22.79 ± 3.15	23.80 ± 3.54	> .05
SBP, mmHg	132.75 ± 19.19	134.62 ± 21.52	133.53 ± 17.03	130.38 ± 18.92	> .05
DBP, mmHg	85.13 ± 13.63	87.86 ± 15.45	84.89 ± 12.16	82.91 ± 12.98	< .05
eGFR, mL/min-1• (1.73m^2)	75.86 ± 33.69	71.63 ± 35.85	75.25 ± 31.89	80.37 ± 32.12	> .05
Hemoglobin, g/L	130.50 ± 20.53	129.96 ± 21.24	130.34 ± 17.97	130.16 ± 21.81	> .05
Serum Creatinine, umol/L	113.01 ± 62.20	127.61 ± 76.26	110.09 ± 55.59	101.53 ± 50.81	< .05
Blood Uric Acid, umol/L	408.11 ± 115.61	421.32 ± 118.96	403.63 ± 117.13	398.23 ± 110.40	> .05
Albumin, g/L	39.34 ± 5.38	36.58 ± 6.07	39.80 ± 4.38	41.53 ± 4.37	< .001
Urine Protein Amount, g/24h	1.66 ± 1.98	2.49 ± 2.35	1.45 ± 1.95	0.98 ± 0.91	< .001
Serum IgA, g/L	2.93 ± 0.96	2.80 ± 0.90	2.89 ± 0.89	3.11 ± 1.08	> .05
Serum IgM, g/L	1.25 ± 0.58	1.20 ± 0.50	1.24 ± 0.62	1.32 ± 0.62	> .05
C3, g/L	1.06 ± 0.21	1.09 ± 0.19	1.06 ± 0.22	1.03 ± 0.21	> .05
C4, g/L	0.26 ± 0.14	0.26 ± 0.10	0.24 ± 0.07	0.28 ± 0.22	> .05

eGFR, estimated glomerular filtration rate; RAS Inhibitor, renin-angiotensin system inhibitor.

into 3 groups: group G1 (sIg G < 8.99g/L, n = 102), group G2 (8.99 ≤ sIgG < 11.17 g/L; n = 103), and group G3 (sIgG > 11.17 g/L, n = 104). The differences in the age, gender, BMI, SBP, eGFR, hemoglobin, serum uric acid, serum IgA, serum IgM, C3, and C4 were not statistically significant among the three groups. Compared with group G1 and group G2, the albumin level was higher in group G3 ($P < .001$) while DBP, serum creatinine level, and 24h proteinuria were lower ($P < .05$).

The correlations between sIgG and blood pressure, proteinuria, serum creatinine, eGFR, pathological IgG level, or pathological IgA grade were shown in Figure 2. The Spearman correlation analysis showed that the sIgG concentration was negatively correlated with 24h proteinuria (r = -0.4002, $P < .001$) and serum creatinine (r = -0.2070, $P < .05$) while not correlated with the eGFR level. The Pearson analysis showed that the sIgG concentration was not associated with SBP and DBP. The T test results showed that sIgG value was negatively associated with glomerular IgG deposition. The patients' baseline histological characteristics were summarized in Table 2. The renal histopathological findings showed significantly differences in the Lee's grade ($P < .001$), tubular atrophy / interstitial fibrosis (T) ($P < .05$), glomerular sclerosis ($P < .05$), proportion of crescent, and renal IgM deposition ($P < .05$) among the three groups ($P < .001$). There were no significant differences in the mesangial hyper cellularity (M), endocapillary hyper cellularity (E), segmental sclerosis (S), renal IgG deposition, and renal C3 deposition ($P > .05$) between groups.

Analysis of Prognostic Risk Factors

The median follow-up time was 33.78 (13.25 to 87) months. 41 patients developed endpoints: 23 cases in group G1 (eGFR < 30%: 9 cases, ESRD: 14 cases); 10 cases in group G2 (eGFR < 30%: 3 cases, ESRD: 7 cases); 8 cases in group G3 (eGFR < 30%: 5 cases, ESRD: 3 cases). The Kaplan-Meier survival analysis showed that the 1-year and 6-year renal survival rates of all participants were 96.09% and 71.91%, respectively. As shown in Figure 3, Kaplan-Meier analysis showed that the cumulative renal survival rates were significantly higher in patients with elevated sIgG level than the patients with lower sIgG level. The 1-year cumulative renal survival rates in group G1, 2, and 3 were 91.97%, 96.8%, and 96.8%. The 6-year cumulative renal survival rates in group G1, 2, and 3 were 41.06%, 68.9%, and 86.56%. The intergroup differences were statistically significant ($P < .05$, Figure 3).

As shown in Table 3, Univariate analysis revealed that DBP, 24h urine proteinuria, blood C3, serum creatinine, glomerular sclerosis ratio, tubular atrophy/interstitial fibrosis, and sIgG decline were the risk factors for unfavorable outcomes.

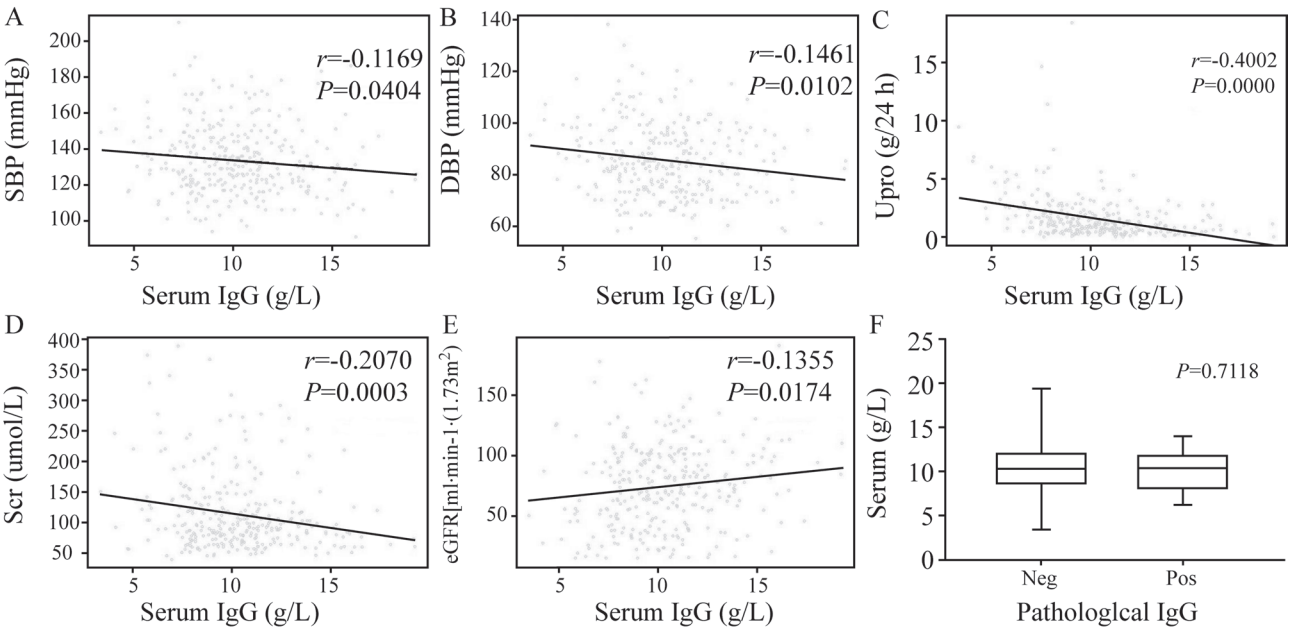

Figure 2. Correlation Analysis Between Serum IgG Concentration and SBP (A), DBP (B), 24h Proteinuria (C), Serum Creatinine (D), eGFR (E), or Renal IgG Deposition (F)

Table 2. Baseline Pathological Data of 309 IgAN Patients

Variable	Sum (n=309)	Serum IgG (g/L)			*P*
		G1 (< 8.99, n = 102)	G2 (8.99 to 11.17, n = 103)	G3 (> 11.17, n = 104)	
Lee's Grade [n (%)]					
1	5 (1.61)	1 (1.00)	2 (1.92)	2 (1.94)	
2	46 (14.89)	8 (8.00)	16 (15.38)	22 (21.36)	
3	150 (48.54)	37 (37.00)	57 (54.81)	56 (54.37)	< .001
4	78 (25.24)	40 (40.00)	19 (18.27)	19 (18.45)	
5	28 (9.06)	14 (14.00)	10 (9.62)	4 (3.88)	
M1 [n (%)]	260 (84.14)	83 (83.00)	85 (81.73)	81 (79.41)	> .05
E1 [n (%)]	93 (30.10)	35 (34.65)	31 (29.81)	25 (24.51)	> .05
S1 [n (%)]	90 (29.13)	25 (24.75)	35 (33.65)	28 (27.18)	> .05
T [n (%)]					
T0	216 (69.90)	59 (58.42)	77 (74.04)	80 (77.67)	
T1	65 (21.03)	30 (29.70)	17 (16.35)	18 (17.48)	< .05
T2	27 (8.74)	12 (11.88)	10 (9.62)	5 (4.85)	
Spherical Sclerosis Ratio	24.64 ± 21.78	29.84 ± 22.71	24.72 ± 21.36	19.49 ± 19.66	< .05
Crescent Ratio	10.41 ± 13.28	14.97 ± 15.98	9.24 ± 12.43	7.29 ± 10.29	< .001
Renal IgG Deposition [n (%)]	14 (4.53)	6 (6.19)	4 (3.88)	4 (3.88)	> .05
Renal IgM Deposition [n (%)]	275 (88.90)	91 (93.81)	90 (86.54)	84 (81.55)	< .05
Renal C3 Deposition [n (%)]	264 (85.43)	88 (90.72)	92 (88.46)	84 (81.55)	> .05

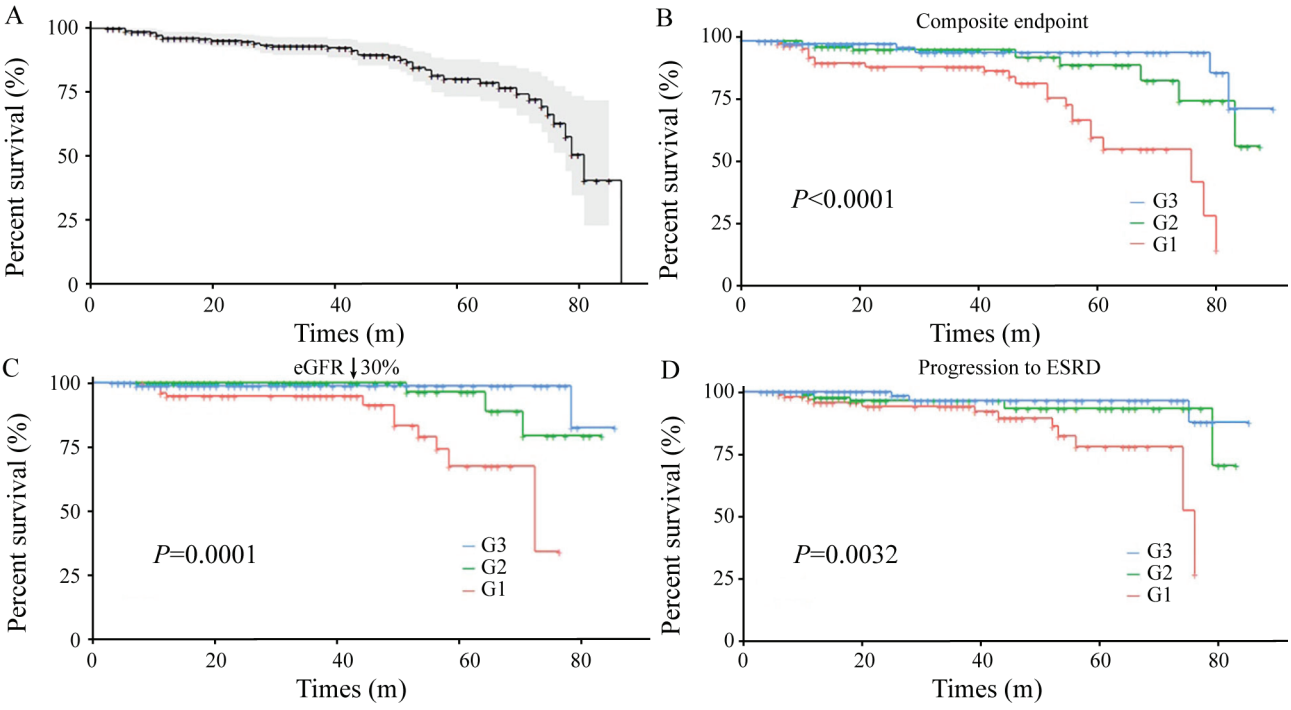

Figure 3. Renal Survival Rate of IgAN Patients in Each Group

The multivariate COX regression analysis showed that, after adjusting for gender, age, BMI, blood pressure, 24h proteinuria, eGFR, M, E, S, T, and crescent in the Oxford grading, each increase in sIgG (by 1g/L) was predictive of renal survival rates with HRs of 0.73 (95% CI: 0.63 to 0.85, $P < .001$), indicating that sIgG served as a possible independent indicator of poor renal outcomes.

As shown in Table 4, The results of further quantitative study of the impact of different sIgG levels on the renal endpoint events of IgAN showed that after adjusted the age, gender, BMI, blood

Table 3. Analysis of Risk Factors for Renal Endpoint Events of IgAN

Variable	Single-factor		Multi-factor	
	HR (95% CI)	*P*	HR (95% CI)	*P*
SBP	1.01 (1.00 to 1.03)	> .05		
DBP	1.02 (1.00 to 1.05)	< .05	1.01 (0.98 to 1.04)	> .05
eGFR	0.98 (0.97 to 0.99)	< .001	0.98 (0.97 to 1.00)	< .05
Hemoglobin	0.99 (0.98 to 1.01)	> .05		
Serum Creatinine	1.01 (1.01 to 1.01)	< .001	1.01 (1.01 to 1.02)	< .001
Uric Acid	1.00 (1.00 to 1.00)	> .05		
Albumin	0.94 (0.90 to 0.99)	< .05	1.00 (0.93 to 0.99)	< .05
24-hr Urine Protein Quantitation	1.12 (1.01 to 1.23)	< .05	1.04 (0.91 to 1.18)	> .05
Serum IgG	0.73 (0.64 to 0.84)	< .001	0.73 (0.63 to 0.85)	< .001
Serum IgA	1.10 (0.79 to 1.53)	> .05		
Serum IgM	0.33 (0.15 to 0.75)	< .05	0.45 (0.17 to 1.23)	> .05
C3	4.30 (1.04 to 17.76)	< .05	2.97 (0.35 to 25.50)	> .05
C4	1.97 (0.39 to 9.91)	> .05		
Spherical Sclerosis Ratio	1.02 (1.01 to 1.04)	< .001	1.01 (0.99 to 1.04)	> .05
Crescent Ratio	1.01 (0.99 to 1.03)	> .05		
Mesangial Hypercellularity	0.78 (0.26 to 2.31)	> .05		
Endocapillary Hypercellularity	1.61 (0.84 to 3.07)	0.1486		
Segment Sclerosis	1.41 (0.74 to 2.67)	0.2985		
Tubular Atrophy/Interstitial Fibrosis	2.46 (1.32 to 4.59)	0.0048	4.70 (2.10 to 10.50)	< .001
Renal IgG Deposition	2.39 (0.73 to 7.88)	0.1512		
Renal IgM Deposition	0.96 (0.40 to 2.30)	0.9244		
Renal C3 Deposition	1.46 (0.52 to 4.12)	0.4745		

Table 4. Hierarchical Analysis of Serum IgG Level with Renal Endpoint Events of IgAN

Variable	Model I			Model II		
	HR (95% CI)	*P*	Trend of *P*	HR (95% CI)	*P*	Trend of *P*
Serum IgG, g/L						
Serum IgG, every < 1 g/L	2.65 (1.30 to 5.38)	< .05		2.74 (1.67 to 4.49)	< .001	
G1 (< 8.99)	7.47 (1.51 to 37.05)	< .05	< .05	6.55 (2.45 to 17.52)	< .001	
G2 (8.99 to 11.17)	3.06 (0.56 to 16.70)	> .05		1.78 (0.61 to 5.18)	> .05	< .001
G3 (> 11.17)	1.0			1.0		

Model 1: after adjusted the age, gender, and BMI.
Model 2: after adjusted the age, gender, BMI, blood pressure, 24-hr urine protein, eGFR, M, E, S, T, and crescent ratio.

pressure, 24h proteinuria, eGFR, M, E, S, T, and crescent ratio, an decrease in sIgG (by 1g/L) was related to the higher risk of development of the endpoints (HR = 2.74, 95% CI: 1.67 to 4.49, $P < .001$). Taking group G3 as a reference, the risk of renal endpoint events was 0.78 times higher in group G2 and 5.55 times higher in group G3 ($P < .05$); that is, as the sIgG decreased, the risk of renal endpoint in IgAN patients increased (Table 4).

DISCUSSION

IgG is the most mass of elements in immunoglobulins, accounting for about 75%. About 40%~50% of the IgG are distributed in the serum and the rest are distributed in tissues. There are four subtypes of IgG: IgG1, IgG2, IgG3, and IgG4. The titers of the above subtypes vary with individuals and time, and they play different roles in the occurrence and development of different autoimmune diseases. Previous studies have shown that[6-8] the antibodies to immune complexes in IgAN are mainly the IgG antibodies. Suzuki *et al.*[6] analyzed the amino acid sequences of IgG that reacts with the Gd-IgA1 and identified an A to S substitution in the complementarity-determining region 3 of the variable region of the gene encoding the IgG heavy chain in IgAN patients. If the alanine is replaced by serine, the affinity of IgG for Gd-IgA1 is significantly increased. Most of Gd-IgA1 in IgAN patients binds to specific IgG antibodies and forms IgA1 immune complexes, which is difficult to be cleared by the liver, thus leading to the abnormal

accumulation of pathogenic Gd-IgA1 complexes.[14] Later, part of the Gd-IgA1 complex deposits in the mesangial area, and these two co-induce mesangial cell proliferation and mesangial matrix increase and stimulate mesangial cells to secrete various inflammatory factors,[15] including: IL-6, MCP-1, or TGF-β, to destroy glomerular intrinsic cells such as mesangial cells,[16,17] podocytes,[18] or tubular epithelial cells,[19] thus being involved in the pathogenesis and progression of IgAN.

In this retrospective study, our data suggest that patients with higher sIgG level have relatively lower DBP, serum creatinine, and 24h proteinuria. Pathologically, patients with higher sIgG level have less tubular atrophy/interstitial fibrosis, proportion of glomerular sclerosis, and proportion of crescent, suggesting that patients with higher sIgG level have milder histological severity. The correlation analysis showed that sIgG value was negatively correlated with 24h proteinuria and serum creatinine, consistent with previous studies.[9,20] In this study, the sIgG value was not associated with renal IgG deposition. It is unclear that whether there is a correlation between sIgG and renal IgG deposition; studies have reported[9] that sIgG level is negatively correlated with renal IgG deposition; but Shin et al[21] has shown that there were no differences in serum IgG concentrations according to the degree of glomerular IgG deposits, which may be related to the duration form onset[22] or whether treatment plans[23] affect the renal IgG deposition. Prognostic analysis in this study found that sIgG decline was associated with deterioration of renal function in patients with IgAN, consistent with the results of Liu *et al*,[10] additionally; it confirmed again that impaired renal function or tubular atrophy/interstitial fibrosis at the time of renal biopsy is an independent risk factor for endpoints in IgAN patients.[24] This study quantified the relationship between sIgG value and renal endpoints in IgAN for the first time, and found that after adjusted the gender, age, BMI, and clinicopathological parameters (blood pressure, 24h proteinuria, eGFR, M/E/S/T of Oxford grade, and ratio of crescent), the risk of renal endpoints increased by 1.74 times for every 1 g/L decline of sIgG value in IgAN patients. In addition, this study also explored the relationship between sIgG level and IgAN progression. The results showed that there was statistical significance in the renal survival rate among the three groups ($P < .05$) when combining the renal endpoint events, eGFR decline by 30%, or progression to ESRD ($P < .05$); that is the lower the patient's sIgG value, the worse the prognosis. Our findings confirm the predictive role of sIgG on renal outcomes in IgAN patients, with patients having lower level of sIgG displaying worse renal survival. There are some possible explanations for the result. First, Gd-IgAl may stimulate the production of both anti-Gd-IgA1-specific IgG antibodies and the other IgG subtypes, thus resulting in changes in the titer and proportion of IgG subtypes. Such changes may affect the pathogenic role of the IgA1 complex to a certain extent. IgG4 has little complement activation ability[25] and has low pathogenicity when combined with Fc segment receptors of phagocytic cells or NK cells. Some scholars[26] found that IgG4 is more likely to inhibit the formation of immune complexes and then limit inflammation response and tissue damage. Therefore, if the titer and proportion of each subtype of sIgG in patients at each stage can be further analyzed, it may help to further understand the occurrence and development of IgAN or provide new targets for the treatment of IgAN. Besides, several studies[15,27] have shown that Gd-IgAl alone is not enough to cause IgAN and must form an immune complex with anti-Gd-IgA1-specific IgG antibody to cause disease. Therefore, high sIgG level may indicate low binding rate with Gd-IgA1, which then decreases the pathogenic ability while causes no obvious glomerular damage. The innovations of this study compared with previous studies are: this study finds that sIgG level can independently affect the occurrence of renal endpoint events of IgAN; sIgG decline suggests a poor prognosis of IgAN. Moreover, quantitative analysis of the impact of sIgG level on renal endpoints of IgAN reveals a 1.74-fold increased risk of renal endpoint events for every 1 g/L reduction in sIgG value.

There are several limitations of this study. First, because it was a retrospective study, there may have many confounding factors. Due to the absence of follow-up data on sIgG concentrations, the changes in sIgG and its correlation with prognosis during follow-up can be confirmed. Second, it was a single-center study, so the source of study cases was single, and the number of samples was limited; furthermore, the follow-up time was shorter

relatively to the progression of IgAN. Large-sample, longer follow-up observation studies are needed to further demonstrate the relationship of sIgG value with the prognosis of IgAN. Third, only the relationship between total sIgG and renal end point events of IgAN was investigated, but the differences among the subtypes (IgG1, IgG2, IgG3, and IgG4) were not further analyzed. Forth, the combination or dose of different therapeutic drugs may affect the sIgG level and renal endpoint events; this study can't further exclude the interference of drug factors. Therefore, the impact of sIgG level on the clinicopathology and prognosis of IgAN remains to be determined by further prospective studies.

CONCLUSION

In summary, we observed that IgAN patients with decreased sIgG at the time of biopsy show more severe clinical and pathological features. Furthermore, sIgG may be helpful in identifying patients who are at risk of poor outcome; with the decrease of sIgG concentration, the risk of renal endpoint events of IgAN increases. Based on the result of our present study, IgAN patients with decreased sIgG at onset have higher risk of disease progression and deserve more attention.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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