



## Research article

## Glomerular IgG deposition predicts kidney disease progression in IgA nephropathy

Yue Xing<sup>a</sup>, Huyan Yu<sup>b</sup>, Hongfen Li<sup>a</sup>, Fanghao Wang<sup>a</sup>, Zhanfei Wu<sup>a</sup>, Wenying Li<sup>a</sup>, Youxia Liu<sup>a,\*</sup>, Junya Jia<sup>a,\*\*</sup>, Tiekun Yan<sup>a</sup><sup>a</sup> Department of Nephrology, Tianjin Medical University General Hospital, Tianjin, China<sup>b</sup> The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, Guangdong Province, China

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## ABSTRACT

**Objective:** We aimed to explore the relationship between the presence and intensity of glomerular IgG deposition and the occurrence of kidney progression events in IgA nephropathy (IgAN).**Methods:** This retrospective study encompassed a total of 1207 patients with IgAN spanning the period from 2010 to 2022, and complete follow-up data were accessible for 736 patients. The IgG intensity was categorized as follows: low-level, defined as IgG (±) and IgG (+), and high-level, defined as IgG (++) and IgG (+++).**Results:** We found that the IgG-positive deposited group (N = 113, 9.36%) had significantly higher levels of ESR, TC, LDL, uric acid, proteinuria, and blood glucose, and lower serum albumin level compared to the IgG-negative deposited group (N = 1094, 90.64%). In terms of pathology, the IgG-positive deposited group had a significantly higher percentage of T2 score compared to the IgG-negative deposited group (p = 0.002). At the end of the follow-up period, the IgG-positive deposited group had a higher eGFR decline ( $-5.7 \pm 4.37$  ml/year) compared to the IgG-negative deposited group ( $-4 \pm 2.52$  ml/year), however, there was not a statistically significant difference between the two groups (p = 0.096). We observed that the high-IgG group had significantly higher level of TG compared to the low-IgG group (p = 0.042). Further analysis revealed that the group of patients with high level of IgG deposition in the kidney experienced a higher incidence of composite kidney outcomes compared to the group with low level of IgG deposition (p = 0.009). Logistic regression analyses showed that high level IgG deposition was an independent risk factor for kidney progression of IgAN (HR 13.419; 95% CI 2.690–66.943, P = 0.029). Further analyses for a solid conclusion using Cox regression that we found high level IgG deposition (HR 115.277; 95% CI 2.299–5.779E3, P = 0.017), eGFR (HR 0.932; 95% CI 0.870–0.999, P = 0.047), and urine protein excretion (HR 1.001; 95% CI 1.000–1.002, P = 0.015) were independent risk factor for kidney progression of IgAN.**Conclusions:** The intensity of IgG deposition has been found to be associated with the progression of IgAN. Future prospective studies should provide more robust evidence on the impact of IgG deposition on kidney outcomes in patients with IgAN.

\* Corresponding author. Department of Nephrology, Tianjin Medical University General Hospital No. 154, Anshan Road, Heping District, Tianjin, China.

\*\* Corresponding author.

E-mail addresses: [5liuyouxia@163.com](mailto:5liuyouxia@163.com) (Y. Liu), [jiajunya@126.com](mailto:jiajunya@126.com) (J. Jia).<https://doi.org/10.1016/j.heliyon.2024.e28509>

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## 1. Introduction

IgA nephropathy (IgAN) is among the most prevalent primary glomerular diseases globally, especially in young Asian adults [1–3]. It is distinguished by a highly dynamic clinical picture that spans from a completely asymptomatic condition to rapid, progressive kidney malfunction. The pathogenesis of IgAN is believed to arise from the deposition of circulating immune complexes (CICs) of composed of IgG bound to galactose-deficient IgA1 (Gd-IgA1) within the glomeruli [4–6]. This deposition triggers mesangial cell proliferation and leads to glomerular injury.

Renal biopsies of IgAN patients are characterized by mesangial IgA dominant or codominant IgG or complement 3 (C3) deposits by routine immunofluorescence microscopy (IFM). There was a growing body of evidence has suggested that IgG autoantibodies in circulation, rather than IgA, played a significant role in the development and prognosis of the disease [7]. The association (Table 6 between IgG staining detected by IFM and disease severity and progression in IgAN remains unclear and requires further investigation to clarify its significance.

In present study, our aim was to investigate the association between mesangial IgG positivity, the intensity of IgG deposition, and kidney progression events in IgAN.

## 2. Materials and methods

This was a retrospective cohort study of IgAN patients at the Tianjin Medical University General Hospital from 2010 to 2022. Among the initial cohort of 1230 patients with biopsy-proven IgAN, patients with other concomitant glomerular diseases including secondary IgA nephropathy, SLE, rheumatic disease, IgA vasculitis, hepatitis B virus-associated GN, liver cirrhosis and patients lacking clinical data were excluded from the study. As a result, a total of 1207 patients were included in the baseline data analysis (Fig. 1). Subsequently, patients lost to follow-up and patients with a follow-up period of less than 12 months were considered as incomplete follow-up further excluded from the study. This led to a final cohort of 736 patients who were included in the follow-up analysis (Fig. 1).

The ethics protocol for the research was approved by the Medical Ethics Committee of the Tianjin Medical University General Hospital (IRB2023-YX-158-01). Informed written consent was provided from all patients.

In this study, the presence of IgG deposits in the mesangium was determined using a direct immunofluorescence assay on frozen sections. The presence of IgG antibodies within the mesangial region was classified as “IgG positive” in this study. Conversely, if there were no deposits observed in the mesangium, classified as “IgG negative.” The IgG intensity was categorized as follows: low-level, defined as IgG ( $\pm$ ) and IgG (+), and high-level, defined as IgG (++) and IgG (+++).

The demographics and clinical data, including Sex, Age, Systolic Blood Pressure (SBP), serum hemoglobin, serum platelets, serum albumin, uric acid, serum creatinine, estimated glomerular filtration rate (eGFR), serum IgA, serum IgG, serum IgE, serum C3, serum C4, erythrocyte sedimentation rate (ESR), total cholesterol (TC), total glyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), blood glucose, urine protein excretion in 24 h, and hematuria were collected at the time of kidney biopsy. All kidney biopsy specimens were reviewed and graded by an independent pathologist who was blind to the participants’ clinical data. The Oxford classification (including crescent scores) was used for the evaluation of pathologic lesions [8]. The eGFR was calculated using

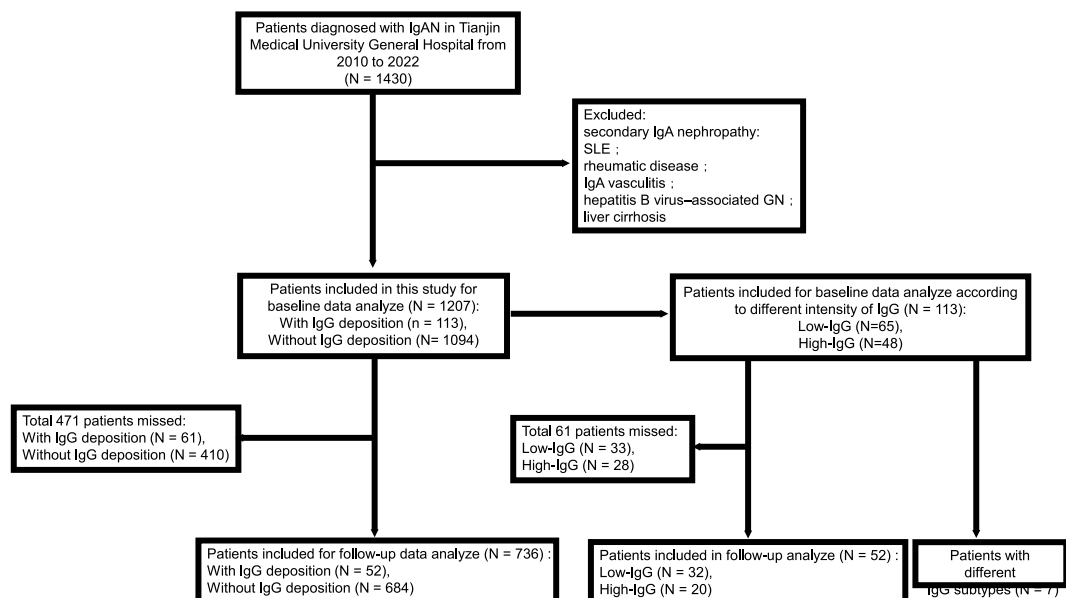


Fig. 1. Flow diagram of the study population.

the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas [9]. The slope of eGFR was defined based on all the eGFR collected during follow-up period and calculated each slope.

Immunosuppressive therapy was defined as treatment with steroids and/or immunosuppressive agents, such as cyclophosphamide, cyclosporine, or mycophenolate mofetil after kidney biopsy. A renin-angiotensin system inhibitor (RASI) therapy was defined as the use of an angiotensin-converting enzyme inhibitor (ACEI) plus/or angiotensin receptor blocker (ARB).

## 2.1. Outcomes

The composite kidney endpoint events were the composite of a doubling of the baseline serum creatinine, 40% reduction in eGFR, end stage renal disease (ESRD, eGFR <15 ml/min per 1.73 m<sup>2</sup>), dialysis, transplant, or death. The rate of kidney function decline was measured by the slope of eGFR per year. Complete remission (CR) is defined as a state where the urinary protein level is less than 500 mg/d, the serum creatinine level remains stable with an increase of no more than 30% from the baseline, and the serum albumin level is within the normal range.

## 2.2. Statistical analyses

Data are expressed as mean ± standard deviation (SD) or numbers and percentages. Non-parametric variables were compared using the Mann-Whitney *U* test. For parameters with a normal distribution, the *t*-test was used to compare the variables. The Chi-square test was employed for comparisons between categorical variables. Logistic regression analysis and Cox regression analysis were used to assess the potential influence of mesangial IgG on the occurrence of kidney progression events in IgAN. A *p*-value of less than 0.05 was considered statistically significant for all analyses conducted in this study. The analysis was performed using SPSS 25.0 software.

**Table 1**

The baseline data for IgAN patients between the IgG-negative deposited group and IgG-positive deposited group.

Characters	Mean ± SD or n (%)		<i>P</i>
	IgG-negative (N = 1094)	IgG-positive (N = 113)	
Male (%)	513(46.9)	49(43.4)	0.474
Age (years)	38.5 ± 12.7	37.1 ± 12.2	0.61
Systolic Blood Pressure (mmHg)	131.4 ± 19.3	131.9 ± 18.9	0.681
Hemoglobin (g/L)	130.1 ± 19.9	130.3 ± 19.4	0.77
Platelets (10 <sup>9</sup> /L)	249.0 ± 65.8	239.3 ± 62.2	0.755
Serum albumin (g/L)	37.36 ± 5.62	35.7 ± 7.36	<0.001
Uric acid (μmol/L)	357.1 ± 92.4	369.1 ± 106.5	0.013
Serum creatinine (μmol/L)	92.35 ± 57.7	91.64 ± 57.7	0.6
eGFR (mL/min/1.73 m <sup>2</sup> )	91.5 ± 31.6	93.4 ± 34.9	0.12
Serum IgA (mg/dL)	320.4 ± 131.7	306.9 ± 114.5	0.839
Serum IgG (mg/dL)	1062.0 ± 283.1	973.1 ± 312.3	0.124
Serum IgE (mg/dL)	168.7 ± 387.4	116.7 ± 256.0	0.195
Serum C3 (mg/dL)	93.1 ± 22.9	94.8 ± 20.6	0.6
Serum C4 (mg/dL)	25.1 ± 54.7	24.5 ± 16.8	0.937
ESR (mm/h)	22.5 ± 16.5	26.4 ± 17.7	0.018
TC (mmol/L)	5.0 ± 1.5	5.3 ± 2.0	0.006
TG (mmol/L)	1.9 ± 1.4	2.0 ± 1.3	0.674
HDL (mmol/L)	1.2 ± 0.5	1.2 ± 0.3	0.703
LDL (mmol/L)	2.9 ± 1.2	3.2 ± 1.5	0.012
Blood glucose (mmol/L)	4.78 ± 0.7	4.95 ± 1.2	0.02
Urine protein excretion (mg/24h)	1758.5 ± 1734.6	2717.2.2 ± 3030.4	<0.001
Hematuria (HP)	77.9 ± 399.8	118.8.2 ± 396.9	0.097
Oxford classification, n(%)			
M (M0/M1)	155(14.1)/939(85.9)	14(12.4)/99(87.6)	0.604
E (E0/E1)	716(65.4)/378(34.6)	68(60.2)/45(39.8)	0.264
S (S0/S1)	398(36.3)/696(63.7)	39(34.5)/74(65.5)	0.694
T (T0/T1/T2)	437(39.9)/446(40.7)/202(19.4)	37(32.7)/39(34.5)/37(32.8)	0.002
C (C0/C1/C2)	397(36.5)/543(50)/145(13.5)	43(38.1)/51(45.1)/19(16.8)	0.485
Treatment			
RASI Treatment, n(%)	438(40.3)	44(39.2)	0.824
immunosuppressive Treatment, n(%)	696(63.6)	71(62.8)	0.129

Abbreviations: M, Male; F, Female; eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; erythrocyte sedimentation rate (ESR); total cholesterol (TC); total glyceride (TG); high density lipoprotein (HDL); low density lipoprotein (LDL); M0, mesangial hypercellularity score of ≤0.5; M1, mesangial hypercellularity score >0.5; E0, absence of endocapillary; E1, presence of endocapillary hypercellularity; S0, absence of segmental glomerulosclerosis; S1, presence of segmental glomerulosclerosis; T0, tubular atrophy/interstitial fibrosis ≤25% of cortical area; T1, tubular atrophy/interstitial fibrosis 26–50% of cortical area; T2, tubular atrophy/interstitial fibrosis >50% of cortical area.

### 3. Results

#### 3.1. Baseline demographic, clinical and pathological information

A total of 1207 primary IgAN patients were recruited in our study, including the IgG-negative group (N = 1094, 90.64%) and IgG-positive group (N = 113, 9.36%). Baseline characteristics in the two groups are summarized in Table 1. Comparing the IgG-negative deposited group, it was found that the IgG-positive deposited group had significantly higher levels of ESR (26.4 ± 17.7 mm/h vs. 22.5 ± 16.5 mm/h,  $p = 0.018$ ), TC (5.3 ± 2.0 mmol/L vs. 5.0 ± 1.5 mmol/L,  $p = 0.006$ ), LDL (3.2 ± 1.5 mmol/L vs. 2.9 ± 1.2 mmol/L,  $p = 0.012$ ), uric acid (369.1 ± 106.5 μmol/L vs. 357.1 ± 92.4 μmol/L,  $p = 0.013$ ), urine protein excretion in 24 h (2717.2 ± 3030.4 mg/24 h vs. 1758.5 ± 1734.6 mg/24 h,  $p < 0.001$ ), and blood glucose (4.95 ± 1.2 mmol/L vs. 4.78 ± 0.7 mmol/L,  $p = 0.002$ ), and lower serum albumin level (35.7 ± 7.36 g/L vs. 37.36 ± 5.62 g/L,  $p < 0.001$ ). In terms of pathology, the IgG-positive deposited group had a significantly higher percentage of T2 scores compared to the IgG-negative deposited group (32.8% vs. 19.4%,  $p = 0.002$ ). There were no significant differences between the two groups in other clinical characters, pathological parameter and the application of RASI (40.3% vs. 39.2%,  $p = 0.824$ ) or immunosuppressive agents (63.6% vs. 62.8%,  $p = 0.129$ ) (Table 1).

#### 3.2. The comparison of IgAN patients between the IgG-negative deposited group and the IgG-positive deposited group

Furthermore, we explored the association between IgG deposition and the kidney progression in IgAN patients with follow-up. A total of 684 IgG-negative deposited patients with a mean follow-up time was 49.2 ± 39.0 months. Additionally, 52 patients with IgG-positive deposition, with a mean follow-up time of 40.2 ± 39.0 months, were also included. Similar to the baseline data comparison in the entire patient populations, the results from patients with follow-up data also showed significantly higher levels of uric acid (373.2

**Table 2**

The comparison of baseline and follow-up data for IgAN patients with follow-up between the IgG-negative deposited group and IgG-positive deposited group.

Characters	Mean ± SD or n (%)		P
	IgG-negative (N = 684)	IgG-positive (N = 52)	
Male (%)	311 (45.4)	24 (46.2)	0.31
Age (years)	38.3 ± 12.6	37.2 ± 11.4	0.612
Systolic Blood Pressure (mmHg)	131.4 ± 18.0	131.6 ± 18.8	0.086
Hemoglobin (g/L)	130.3 ± 20.3	130 ± 19.6	0.874
Platelets (10 <sup>9</sup> /L)	253.8 ± 67.2	244.2 ± 60.4	0.653
Serum albumin (g/L)	37.4 ± 5.38	35.24 ± 7.17	0.001
Uric acid (μmol/L)	352.3 ± 87.3	373.2 ± 105.4	0.032
Serum creatinine (μmol/L)	92.0 ± 58.3	88.6 ± 53.1	0.765
eGFR (mL/min/1.73 m <sup>2</sup> )	91.1 ± 30.9	95.6 ± 32.0	0.812
Serum IgA (mg/dL)	326.5 ± 140.9	315.2 ± 95.1	0.468
Serum IgG (mg/dL)	1052.8 ± 262.7	987.2 ± 263.6	0.72
Serum IgE (mg/dL)	155.4 ± 384.5	102.9 ± 178.3	0.278
Serum C3 (mg/dL)	92.9 ± 21.4	94.9 ± 22.9	0.208
Serum C4 (mg/dL)	26.6 ± 68.8	27.6 ± 23.8	0.921
ESR (mm/h)	22.0 ± 17.8	26.3 ± 17.2	0.242
TC (mmol/L)	5.0 ± 1.4	5.3 ± 1.9	0.052
TG (mmol/L)	1.9 ± 1.5	2.0 ± 1.5	0.698
HDL (mmol/L)	1.2 ± 0.5	1.2 ± 0.3	0.814
LDL (mmol/L)	2.9 ± 1.2	3.1 ± 1.5	0.054
Blood glucose (mmol/L)	4.8 ± 0.8	5.0 ± 1.2	0.054
Urine protein excretion (mg/24h)	1779.6 ± 1700.9	2698.2 ± 2988.7	<0.001
Hematuria (HP)	79.9 ± 459.2	68.1 ± 171.7	0.753
Oxford classification, n (%)			
M (M0/M1)	84 (12.3)/595 (87.7)	2 (3.8)/50 (96.2)	0.066
E (E0/E1)	408 (59.6)/271 (40.4)	28 (53.8)/24 (46.2)	0.377
S (S0/S1)	236 (34.5)/443 (65.5)	15 (28.8)/37 (71.2)	0.387
T (T0/T1/T2)	261 (38.1)/301 (44)/117 (17.9)	17 (32.7)/21 (40.4)/14 (26.9)	0.21
C (C0/C1/C2)	211 (30.8)/363 (53)/105 (16.2)	14 (26.9)/28 (53.8)/10 (19.3)	0.702
Time (months)	49.2 ± 39.0	67.6 ± 42.2	0.39
The slope of eGFR	-4 ± 2.52	-5.7 ± 4.37	0.096
Achievement of CR, n (%)	522 (76.3)	41 (78.9)	0.678
The composite kidney endpoint events, n (%)	88 (12.9)	7 (13.5)	0.902
Treatment			
RASI Treatment, n (%)	253 (37.3)	21 (41.1)	0.583
immunosuppressive Treatment, n (%)	477 (69.7)	37 (72.5)	0.271

Abbreviations: M, Male; F, Female; eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; erythrocyte sedimentation rate (ESR); total cholesterol (TC); total glyceride (TG); high density lipoprotein (HDL); low density lipoprotein (LDL); complete remission (CR); The composite kidney endpoint events: a doubling of the baseline serum creatinine, 40% reduction in eGFR, ESRD (eGFR <15 ml/min/1.73 m<sup>2</sup>), or death.

$\pm 105.4 \mu\text{mol/L}$  vs.  $352.3 \pm 87.3 \mu\text{mol/L}$ ,  $p = 0.032$ ) and urine protein excretion in 24 h ( $2698.2 \pm 2988.7 \text{ mg/24 h}$  vs.  $1779.6.2 \pm 1700.9 \text{ mg/24 h}$ ,  $p < 0.001$ ), while lower serum albumin level in the IgG-positive deposited group ( $35.24 \pm 7.17 \text{ g/L}$  vs.  $37.4 \pm 5.38 \text{ g/L}$ ,  $p = 0.001$ ). At the end of the follow-up period, it was observed that the IgG-positive deposited group had a higher eGFR decline ( $-5.7 \pm 4.37 \text{ ml/year}$ ) compared to the IgG-negative deposited group ( $-4 \pm 2.52 \text{ ml/year}$ ), however, it did not reveal a statistically significant difference between the two groups ( $p = 0.096$ ). In addition, there were no significant differences between the two groups in terms of CR rates ( $76.3\%$  vs.  $78.9\%$ ,  $p = 0.678$ ) and the composite kidney endpoint events rates ( $12.9\%$  vs.  $13.5\%$ ,  $p = 0.902$ ). The detailed information above can be found in [Table 2](#).

### 3.3. The comparison of IgAN patients between the low-IgG group and the high-IgG group

We subsequently divided the patients into two groups: the low-IgG group ( $N = 65$ ) and the high-IgG group ( $N = 48$ ). Baseline characteristics in the two groups are summarized in [Table 3](#). We observed that the high-IgG group exhibited significantly higher level of TG compared to the low-IgG group ( $2.0 \pm 1.6 \text{ mmol/L}$  vs.  $2.0 \pm 1.1 \text{ mmol/L}$ ,  $p = 0.042$ ). However, there were no significant differences observed between the two groups for the other items analyzed.

Among the 52 patients with complete follow-up data, 32 were in the low-IgG deposition group, with a mean follow-up duration of  $58.8 \pm 40.5$  months, while 20 patients were in the high-IgG deposition group, with a mean follow-up duration of  $80.2 \pm 42.4$  months. The results showed that the group of patients with high levels of IgG deposition in the kidneys experienced a higher incidence of composite kidney outcomes compared to the group with low levels of IgG deposition, indicated in [Table 4](#) ( $40\%$  vs.  $9.4\%$ ,  $p = 0.009$ ). However, there were no significant differences in the slope of eGFR and the percentage of CR between the two groups, The detailed information showed in [Table 4](#).

### 3.4. Risk factors for kidney disease progression in IgAN patients

Logistic regression analyses were conducted to examine the potential risk factors affecting kidney disease progression in IgAN patients. The results indicated that a high intensity of IgG deposition (HR 13.419; 95% CI 2.690–66.943,  $P = 0.029$ ) was identified as a

**Table 3**

The baseline data for IgAN patients between the low-IgG group and the high-IgG group.

Characters	Mean $\pm$ SD or n(%)		P
	Low-IgG (N = 65)	High-IgG (N = 48)	
Male (%)	27(41.5)	22(45.8)	0.649
Age (years)	$38.6 \pm 12.9$	$35.1 \pm 10.9$	0.129
Systolic Blood Pressure (mmHg)	$131.9 \pm 19.3$	$131.8 \pm 18.4$	0.829
Hemoglobin (g/L)	$130.9 \pm 19.35$	$130 \pm 19.4$	0.775
Platelets ( $10^9/L$ )	$238.6 \pm 59.3$	$239.9 \pm 65.9$	0.177
Serum albumin (g/L)	$34.9 \pm 7.6$	$36.7 \pm 7.2$	0.195
Uric acid ( $\mu\text{mol/L}$ )	$354.7 \pm 92.2$	$361.2 \pm 87.3$	0.708
Serum creatinine ( $\mu\text{mol/L}$ )	$89.6 \pm 63.2$	$94.7 \pm 46.9$	0.637
eGFR ( $\text{mL/min/1.73 m}^2$ )	$95.5 \pm 34.5$	$90.4 \pm 35.6$	0.445
Serum IgA (mg/dL)	$324.2 \pm 128.1$	$306.4 \pm 97.2$	0.514
Serum IgG (mg/dL)	$984.4 \pm 314.6$	$956.3 \pm 312.1$	0.865
Serum IgE (mg/dL)	$139.3 \pm 316.9$	$86.8 \pm 139.2$	0.121
Serum C3 (mg/dL)	$94.9 \pm 21.9$	$97.6 \pm 22.6$	0.615
Serum C4 (mg/dL)	$23.3 \pm 9.4$	$35.4 \pm 47.4$	0.177
ESR (mm/h)	$30.3 \pm 18.7$	$20.3 \pm 14.1$	0.245
TC (mmol/L)	$5.3 \pm 2.1$	$5.1 \pm 1.7$	0.731
TG (mmol/L)	$2.0 \pm 1.1$	$2.0 \pm 1.6$	0.042
HDL (mmol/L)	$1.1 \pm 0.3$	$1.2 \pm 0.4$	0.136
LDL (mmol/L)	$3.2 \pm 1.5$	$3.1 \pm 1.5$	0.481
Blood glucose (mmol/L)	$4.93 \pm 1.01$	$4.98 \pm 1.53$	0.503
Urine protein excretion (mg/24h)	$2555 \pm 2300$	$2517 \pm 2637$	0.524
Hematuria (HP)	$137.1 \pm 486.6$	$92.9 \pm 218.5$	0.215
Oxford classification, n(%)			
M (M0/M1)	9(13.8)/56(86.2)	5(10.4)/43(89.6)	0.584
E (E0/E1)	40(61.5)/25(38.5)	28(16.7)/20(83.3)	0.731
S (S0/S1)	21(32.3)/44(67.7)	18(37.5)/30(62.5)	0.566
T (T0/T1/T2)	21(32.3)/22(33.8)/23(33.9)	16(12.5)/17(35.4)/14(52.1)	0.852
C (C0/C1/C2)	24(36.9)/29(44.6)/12(18.5)	19(39.6)/22(45.8)/7(14.6)	0.858
Treatment			
RASI Treatment, n(%)	27(41.5)	17(36.2)	0.566
immunosuppressive Treatment, n(%)	48(73.8)	29(60.4)	0.195

Abbreviations: M, Male; F, Female; eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; erythrocyte sedimentation rate (ESR); total cholesterol (TC); total glyceride (TG); high density lipoprotein (HDL); low density lipoprotein (LDL); Low-IgG: including IgG( $\pm$ ) and IgG(+), High-IgG: including IgG(++) and IgG(+++).

**Table 4**

The comparison of baseline and follow-up data for IgAN patients with follow-up between the low-IgG group and the high-IgG group.

Characters	Mean ± SD or n (%)		P
	Low-IgG (N = 32)	High-IgG (N = 20)	
Male n (%)	14 (43.7)/18 (56.3)	9 (45)/11 (55)	0.93
Age (years)	38 ± 11.76	35.9 ± 10.86	0.522
Systolic Blood Pressure (mmHg)	131.3 ± 16.4	132.1 ± 22.7	0.107
Hemoglobin (g/L)	130.9 ± 19.35	130 ± 19.4	0.775
Platelets (10 <sup>9</sup> /L)	235.7 ± 52.2	257.3 ± 70.6	0.071
Serum albumin (g/L)	36.6 ± 7.3	34.4 ± 7.1	0.306
Uric acid (μmol/L)	346.8 ± 78.4	354.9 ± 87.2	0.729
Serum creatinine (μmol/L)	83.3 ± 45	95.5 ± 58.8	0.406
eGFR (mL/min/1.73 m <sup>2</sup> )	95.5 ± 34.5	90.4 ± 35.6	0.445
Serum IgA (mg/dL)	324.2 ± 128.1	306.4 ± 97.2	0.514
Serum IgG (mg/dL)	990.9 ± 271.9	981.3 ± 257.8	0.926
Serum IgE (mg/dL)	119.9 ± 210.0	76.8 ± 116.4	0.233
Serum C3 (mg/dL)	94.9 ± 21.9	97.6 ± 22.6	0.615
Serum C4 (mg/dL)	23.3 ± 9.4	35.4 ± 47.4	0.177
ESR (mm/h)	28.4 ± 18.6	22.5 ± 14.4	0.472
TC (mmol/L)	5.3 ± 1.9	5.3 ± 2.1	0.869
TG (mmol/L)	1.8 ± 1.1	2.3 ± 2.1	0.008
HDL (mmol/L)	1.2 ± 0.31	1.3 ± 0.3	0.58
LDL (mmol/L)	3.1 ± 1.2	3.2 ± 1.8	0.091
Blood glucose (mmol/L)	5.00 ± 1.1	5.01 ± 1.3	0.91
Urine protein excretion (mg/24h)	2325.3 ± 2981.1	2914.7 ± 3020.6	0.229
Hematuria (HP)	71.8 ± 215.6	62.8 ± 76.3	0.475
Oxford classification, n (%)			
M (M0/M1)	1 (3.1)/31 (96.9)	1 (5.0)/19 (95)	0.732
E (E0/E1)	17 (53.1)/15 (46.9)	11 (55)/9 (45)	0.895
S (S0/S1)	7 (21.8)/25 (78.2)	8 (40)/12 (60)	0.16
T (T0/T1/T2)	9 (28.1)/13 (40.6)/10 (31.3)	8 (40)/8 (40)/4 (20)	0.574
C (C0/C1/C2)	10 (31.2)/15 (46.8)/7 (22)	4 (20)/13 (65)/3 (15)	0.442
Time (months)	58.8 ± 40.5	80.2 ± 42.4	0.827
The slope of eGFR	-1.46 ± 10.9	-2.16 ± 6.9	0.157
Achievement of CR, n (%)	12 (37.5)	9 (45)	0.592
The composite kidney endpoint events, n (%)	3 (9.4)	8 (40)	0.009
Treatment			
RASI Treatment, n (%)	15 (46.8)	6 (31.6)	0.283
immunosuppressive Treatment, n (%)	25 (78.1)	16 (80.0)	0.641

Abbreviations: M, Male; F, Female; eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; erythrocyte sedimentation rate (ESR); total cholesterol (TC); total glyceride (TG); high density lipoprotein (HDL); low density lipoprotein (LDL); complete remission (CR); The composite kidney endpoint events: a doubling of the baseline serum creatinine, 40% reduction in eGFR, ESRD (eGFR <15 ml/min/1.73 m<sup>2</sup>), or death.

**Table 5**

Regression analysis of possible factors that contributed to kidney progression events in IgA nephropathy.

Parameter	Univariate analysis			Multivariate analysis		
	B	95%CI	P value	B	95%CI	P value
Systolic Blood Pressure (mmHg)	1.032	[0.998,1.067]	0.064			
Platelets (10 <sup>9</sup> /L)	1.005	[0.995,1.015]	0.351			
Serum albumin (g/L)	1.014	[0.934,1.100]	0.739			
Uric acid (μmol/L)	1.003	[0.996,1.010]	0.449			
Serum creatinine (μmol/L)	1.007	[0.996,1.019]	0.202			
eGFR (mL/min/1.73 m <sup>2</sup> )	0.99	[0.971,1.009]	0.292	0.994	[0.997,1.019]	0.628
Serum IgA (mg/dL)	0.994	[0.986,1.002]	0.132			
Serum IgG (mg/dL)	0.998	[0.996,1.001]	0.229			
ESR (mm/h)	0.983	[0.927,1.042]	0.558			
TG (mmol/L)	1.418	[0.928,2.167]	0.106			
LDL (mmol/L)	1.577	[0.997,2.494]	0.051			
Urine protein excretion (mg/24h)	1.000	[1.000,1.000]	0.554	1.000	[1.000,1.000]	0.402
Hematuria (HP)	0.999	[0.993,1.004]	0.595			
T score (T0 vs T1/T2)			0.741			
M score (M1 vs M2)			0.999			
C score (C0 vs C1/C2)			0.769			
Groups in different deposition intensity of IgG (Low/High)	14.5	[3.275,64.190]	<0.0001	13.419	[2.690,66.943]	0.002

Abbreviations: eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; erythrocyte sedimentation rate (ESR); total glyceride (TG); low density lipoprotein (LDL); The IgG intensity was defined as low: IgG (±) and IgG (+), and high: IgG (++) and IgG (+++).

risk factor for the progression of kidney disease in IgAN even after adjusted for eGFR and urine protein excretion (Table 5)). Further analyses for a solid conclusion using Cox regression that we found high level IgG deposition (HR 115.277; 95% CI 2.299–5.779E3,  $P = 0.017$ ), eGFR (HR 0.932; 95% CI 0.870–0.999,  $P = 0.047$ ), and urine protein excretion (HR 1.001; 95% CI 1.000–1.002,  $P = 0.015$ ) were independent risk factor for kidney progression of IgAN (Table 6).

#### 4. Discussion

IgAN is currently recognized as an autoimmune disorder in which circulating immune complexes (ICs) composed of IgA and IgG antibodies, or the formation of ICs directly within the kidney (in situ), can deposit in the mesangial area [10]. This deposition of ICs in the mesangial region contributes to the development and progression of IgAN. The study conducted by Zina et al. demonstrated that immunodeficient mice injected with Gd-IgA1 mixed with IgG autoantibodies derived from patients with IgAN exhibited glomerular injury accompanied by symptoms of hematuria and proteinuria [11]. In contrast, the ICs formed by mixing Gd-IgA1 with IgG from healthy individuals did not induce any pathological changes. These findings provide evidence for the pathogenic role of IgG antibodies in IgAN.

Regarding IgG deposition rates in patients with IgAN, concomitant IgG was variably deposited from approximately 10-80% in patients with IgA nephropathy [12]. Haas demonstrated an IgG deposition rate of approximately 45% [13]. Similarly, Okada et al. observed an IgG deposition rate of 50% in a study involving 111 Japanese patients with IgAN [14]. Furthermore, one study found that IgG in renal immunodeposits of IgAN is enriched with autoantibodies specific for Gd-IgA1. The authors showed that IgG specific for Gd-IgA1 was extracted from remnant IgAN kidney-biopsy specimens and glomerular colocalization of IgG and IgA using by confocal microscopy, even when IgG was not detected by routine immunofluorescence [15]. In our department, the overall rate of IgG-positive deposition is approximately 9.7%, which is lower compared to the broader range mentioned in the literature.

Previous studies have identified several prognostic factors that are significantly associated with poor clinical outcomes in IgAN. These factors include elevated serum creatinine, massive proteinuria, hypertension, glomerular sclerosis and interstitial fibrosis [16]. The impact of IgG deposition on the severity and progression of IgAN remains uncertain or not well-established. There are some researches suggesting that the deposition of IgG in the glomerular mesangial space and glomerular capillary loops is associated with poor prognostic factors in IgAN. Nieuwhof, C. et al. Showed the co-deposition of IgG with IgA in the mesangial area has been identified as a significant risk factor for kidney progression in patients with IgAN [17]. Additionally, the results of Wada's study suggested that mesangial IgG deposition could be valuable in evaluating disease activity and predicting the effectiveness of treatment in IgAN patients [18]. These findings emphasize the potential significance of kidney IgG deposition in understanding the severity, progression, and management of IgAN. However, the study conducted by Bellur et al. didn't find a relationship between glomerular IgG positivity and worse renal outcomes [19]. In our study, the results showed the presence of glomerular IgG deposition was associated with higher levels of ESR, TC, LDL, uric acid, proteinuria, blood glucose, and lower serum albumin level. Furthermore, the patients with glomerular IgG deposition had a relatively rapid decline in eGFR, although not reaching statistical significance. However, no significant difference was found between the presence and absence of glomerular IgG deposition in relation to composite kidney endpoint events rates.

Some researchers have investigated whether the intensity of IgG staining could have an impact on the kidney outcomes in IgAN. In one study, no correlation was found between the intensity of IgG staining and various clinical parameters and Oxford scores in IgAN [20]. A Japanese cohort study reported an opposite conclusion that the intensity of IgG in the capillary loops was associated with a decrease in eGFR [21]. This finding suggests that a higher intensity of IgG deposition in the glomerulus may be linked to a worse renal prognosis in IgAN. In our study, the results indicated that patients with a high grade of IgG deposition had a worse prognosis and a higher percentage of patients experienced disease progression. Furthermore, the results of multivariate logistic regression analysis demonstrated that the intensity of IgG deposition was associated with a poorer prognosis of the disease. This suggests that the severity or intensity of IgG deposition in the glomeruli may have an impact on the progression of IgAN and could be considered as a prognostic factor [20]. The greater potential of IgG deposits to initiate and sustain an inflammatory process may accelerate the progression of IgAN. Further research is needed to better understand the underlying mechanisms and the clinical implications of IgG deposition in IgAN.

Bannister et al. found predominantly IgG1 deposition in 20 patients with IgAN [22]. They also observed that higher levels of serum IgG1 were found in IgAN, suggesting a potential link between circulating immune complexes and glomerular deposition. Kawasaki, Y. et al. Observed mesangial deposits in IgAN predominantly consisted of IgG1 (81% of the studied biopsies) and IgG3 (64%) [23].

**Table 6**

Cox regression analysis of possible factors that contributed to kidney progression events in IgA nephropathy.

Parameter	Univariate analysis			Multivariate analysis		
	B	95%CI	P value	B	95%CI	P value
eGFR (mL/min/1.73 m <sup>2</sup> )	0.964	[0.943,0.985]	0.001	0.932	[0.870,0.999]	0.047
Urine protein excretion (mg/24h)	1.000	[1.000,1.000]	0.002	1.001	[1.000,1.002]	0.015
T score (T0 vs T1/T2)			0.281			0.627
C score (C0 vs C1/C2)			0.074			0.388
Groups in different deposition intensity of IgG (Low/High)	3.985	[1.053,15.076]	0.042	115.277	[2.299,5.779E3]	0.017

Abbreviations: eGFR: using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas; The IgG intensity was defined as low: IgG (±) and IgG (+), and high: IgG (++) and IgG (+++).

However, IgG2 was found in only one out of the 11 cases studied, and IgG4 was not detected at all in the observed deposits. Their study did not find a correlation between the identified IgG subtypes and the presence of mesangial complement proteins, the severity of mesangial lesions, or the clinical data including serum creatinine levels, proteinuria, and hematuria. In our center, we have data on seven patients who were detected using a direct immunofluorescence assay on frozen sections in September 2021. Among these patients, the predominant IgG subclasses are IgG1 and IgG3, while only two patients show IgG4 deposition. Interestingly, all patients have negative IgG2 deposition in the kidney (Supplement Table 1). This observation further strengthens the evidence that IgG1 and IgG3 may play a significant role in the disease process of IgAN. However, the underlying mechanisms for the restrictions observed in the kidney, such as why IgA-IgG1 and IgA-IgG3 are favored to deposit needed further explanation.

There are some limitations in our study. Firstly, the numbers of patients with glomerular IgG deposits and IgG subtypes were limited, and this small sample size can potentially hinder the generalizability of the findings and weaken the statistical power to identify significant associations. Secondly, the short duration of follow-up and a high number of patients lost to follow-up can induce bias and affect the ability to assess long-term outcomes accurately. Thirdly, there are potential confounding factors that can influence the relationship between IgG deposition and the progression of renal disease in IgAN, which may impact the interpretation of the findings.

Future prospective studies should aim to address the limitations of small sample sizes and short follow-up periods to provide more robust evidence on the impact of IgG deposition on kidney outcomes in patients with IgAN.

## 5. Conclusion

The intensity of IgG deposition has been found to be associated with the progression of IgAN. Future prospective studies should provide more robust evidence on the impact of IgG deposition on kidney outcomes in patients with IgAN.

## Ethics approval and consent to participate

All subjects provided written informed consents. The study protocol was in adherence with the Declaration of Helsinki and was approved by the Institutional Ethical Committee of Tianjin Medical University General Hospital.

## Consent for publication

Not applicable.

## Availability of data and materials

Raw data used during the current study are available from the corresponding author on reasonable request for non-commercial use.

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## Data availability statement

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

## CRedit authorship contribution statement

**Yue Xing:** Writing – original draft, Formal analysis, Data curation. **Huyan Yu:** Formal analysis, Data curation. **Hongfen Li:** Data curation. **Fanghao Wang:** Data curation. **Zhanfei Wu:** Data curation. **Wenyong Li:** Data curation. **Youxia Liu:** Supervision, Project administration, Conceptualization. **Junya Jia:** Supervision, Project administration. **Tiekun Yan:** Supervision, Project administration.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e28509>.

## References

- [1] G. D'Amico, The commonest glomerulonephritis in the world: IgA nephropathy, *Q. J. Med.* 64 (245) (1987) 709–727.
- [2] K.T. Woo, et al., A global evolutionary trend of the frequency of primary glomerulonephritis over the past four decades, *Kidney Dis.* 5 (4) (2019) 247–258.
- [3] A. McGrogan, C.F. Franssen, C.S. de Vries, The incidence of primary glomerulonephritis worldwide: a systematic review of the literature, *Nephrol. Dial. Transplant.* 26 (2) (2011) 414–430.
- [4] H. Suzuki, et al., The pathophysiology of IgA nephropathy, *J. Am. Soc. Nephrol.* 22 (10) (2011) 1795–1803.
- [5] R.J. Wyatt, B.A. Julian, IgA nephropathy, *N. Engl. J. Med.* 368 (25) (2013) 2402–2414.
- [6] R. Coppo, et al., Aberrantly glycosylated IgA1 induces mesangial cells to produce platelet-activating factor that mediates nephrin loss in cultured podocytes, *Kidney Int.* 77 (5) (2010) 417–427.
- [7] W.J. Placzek, et al., Serum galactose-deficient-IgA1 and IgG autoantibodies correlate in patients with IgA nephropathy, *PLoS One* 13 (1) (2018) e0190967.
- [8] 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.
- [9] X. Kong, et al., Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating glomerular filtration rate in the Chinese population, *Nephrol. Dial. Transplant.* 28 (3) (2013) 641–651.
- [10] J. Novak, et al., IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells, *Kidney Int.* 67 (2) (2005) 504–513.
- [11] Z. Moldoveanu, et al., Experimental evidence of pathogenic role of IgG autoantibodies in IgA nephropathy, *J. Autoimmun.* 118 (2021) 102593.
- [12] D.M. Silverstein, et al., Sequential occurrence of IgA nephropathy and Henoch-Schönlein purpura: support for common pathogenesis, *Pediatr. Nephrol.* 8 (6) (1994) 752–753.
- [13] M. Haas, Histology and immunohistology of IgA nephropathy, *J. Nephrol.* 18 (6) (2005) 676–680.
- [14] K. Okada, et al., IgA nephropathy in Japanese children and adults: a comparative study of clinicopathological features, *Am. J. Nephrol.* 10 (3) (1990) 191–197.
- [15] D.V. Rizk, et al., Glomerular immunodeposits of patients with IgA nephropathy are enriched for IgG autoantibodies specific for galactose-deficient IgA1, *J. Am. Soc. Nephrol.* 30 (10) (2019) 2017–2026.
- [16] G. D'Amico, Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome, *Semin. Nephrol.* 24 (3) (2004) 179–196.
- [17] C. Nieuwhof, et al., Chronicity index and mesangial IgG deposition are risk factors for hypertension and renal failure in early IgA nephropathy, *Am. J. Kidney Dis.* 31 (6) (1998) 962–970.
- [18] 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.
- [19] 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.
- [20] K. Turgutalp, et al., The relationship between glomerular IgG staining and poor prognostic findings in patients with IgA nephropathy: the data from TSN-GOLD working group, *BMC Nephrol.* 22 (1) (2021) 352.
- [21] Y. Kobayashi, et al., IgA nephropathy: prognostic significance of proteinuria and histological alterations, *Nephron* 34 (3) (1983) 146–153.
- [22] K.M. Bannister, et al., Glomerular IgG subclass distribution in human glomerulonephritis, *Clin. Nephrol.* 19 (4) (1983) 161–165.
- [23] Y. Kawasaki, et al., Evaluation of T helper-1/2 balance on the basis of IgG subclasses and serum cytokines in children with glomerulonephritis, *Am. J. Kidney Dis.* 44 (1) (2004) 42–49.