Int J Clin Exp Pathol 2017;10(10):10475-10482
www.ijcep.com /ISSN:1936-2625/IJCEP0060564

Original Article

Elevated baseline serum IgA may predict earlier proteinuria remission in IgA nephropathy patients

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Received June 30, 2017; Accepted August 5, 2017; Epub October 1, 2017; Published October 15, 2017

Abstract: The goals of this work were to investigate the correlations of elevated serum IgA with renal pathology and outcome of proteinuria in IgA nephropathy patients. Retrospective cohort analysis enrolled 90 IgA nephropathy patients (proteinuria ≥0.5 g/24 hr, estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2) who were admitted to The Sixth Affiliated Hospital of Sun Yat-sen University from 2013.01 to 2017.04. The elevated serum IgA level was found in 20 (22.2%) patients. In clinical characteristics, serum IgG, ratio of IgA/C3 and recurrent mucosal infection rate were increased obviously in high serum IgA group compared with normal serum IgA group (serum IgG, 14.90±3.50 g/L *vs.* 10.27±3.49 g/L, P<0.001, IgA/C3, 4.45±1.21 *vs.* 2.77±0.75, P<0.001, recurrent mucosae infection rate, 40.0% *vs.* 14.3%, P=0.027). In kidney biopsy, mesangial proliferation was significantly more common in normal serum IgA group (81% *vs.* 50% in high serum IgA group, P=0.028). The proportion of crescent less than 25% more often occurred in elevated IgA group (81.3% *vs.* 63.8% in normal IgA group). The Kaplan-Meier curves showed that proteinuria remission rate for patients with high serum IgA was 80%, 85%, 90%, 95% and 95% after 3, 6, 9, 12 and 15 months compared with patients with normal serum IgA (proteinuria remission rate, 45%, 64%, 75%, 86% and 93%, P=0.020). Cox proportional hazard regression model indicated that elevated serum IgA (RR=1.984, P=0.040) and steroids therapy (RR=2.192, P=0.030) were independent predictors for proteinuria remission in IgA nephropathy patients. In view of our data, more active treatments may improve outcome of IgA nephropathy patients with elevated serum IgA. We conclude that elevated serum IgA may indicate a higher proteinuria remission rate within a shorter period of time in IgA nephropathy patients.

Keywords: IgA nephropathy, serum IgA, proteinuria, pathology, prognosis, mucosal infection

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world at present [1]. There was a higher IgAN incidence rate in the East Asia region, for instance, IgAN accounted for about 40% of all primary glomerulopathy in in China and Japan [1, 2]. The range of clinical manifestations of IgAN is broad, from asymptomatic microscopic hematuria to rapidly progressive glomerular nephropathy [3]. Massive proteinuria, renal dysfunction and severe renal histological injury are vital risk factors that affect the prognosis of IgA nephropathy [4]. Wenge Li confirmed that baseline proteinuria levels of >0.5 g/24 h and more severe pathological injury significantly influenced the probability of adverse events in IgAN patients [5].

Helin H reported that 50%-70% IgAN patients complicated with elevated serum IgA [6]. However, the relationships between increased IgA with clinical features, renal pathology and prognosis of IgAN patients are still unclear. Recently, a retrospective study indicated that the elevated serum IgA at baseline might be associated with mesangial proliferation and segmental sclerosis contributed to glomerulosclerosis, but had no effect on the presence of proteinuria or on the worsening of kidney function in children with IgA nephropathy [7]. Nevertheless, the correlations of elevated serum IgA with renal pathology and outcome in adult IgAN patients have not been explored. The aim of present study was to determine the relationships between increased IgA with clinical features, renal pathology and treatment outcomes of adult IgAN patients with proteinuria.

Table 1. Clinical baseline data of enrolled patients

Variable	Normal IgA group n=70	Elevated IgA group n=20	*P*-value
Age (years)	33.67±10.97	38.1±12.58	0.127
Gender, male [n (%)]	39 (55.7)	9 (45.0)	0.397
BMI (Kg/m^2)	23.37±3.79	23.24±4.01	0.899
Hypertension [n (%)]	31 (44.3)	8 (40.0)	0.733
Macrohematuria [n (%)]	8 (11.4)	2 (10.0)	1.000
RBC (× 10E12/L)	4.34±0.92	4.09±0.70	0.267
Hemoglobin (g/L)	126.96±24.41	121.80±23.70	0.401
Serum calcium (mmol/L)	2.28±0.18	2.31±0.17	0.442
Serum phosphorus (mmol/L)	1.25±0.25	1.13±0.22	0.051
Serum creatinine (μmol/L)	110.84±45.78	112.63±39.65	0.875
Blood urea nitrogen (mmol/L)	6.61±2.77	7.39±2.67	0.259
Serum uric acid (μmol/L)	432.49±114.17	443.06±109.86	0.709
Microhematuria (+)	2 (1, 2)	2 (1, 3)	0.892
Proteinuria dipstick (+)	2 (1, 3)	2 (1, 3)	0.712
Proteinuria quantifcation (g/24 h)	1.4 (0.64, 3.08)	0.98 (0.68, 1.69)	0.277
Serum albumin (g/L)	37.44±7.56	39.51±6.73	0.271
Serum cholesterol (mmol/L)	5.79±1.66	5.18±1.46	0.187
Serum IgG (g/L)	10.27±3.49	14.90±3.50	<0.001
Serum IgM (g/L)	1.35±0.67	1.49±0.85	0.438
Serum C3 (g/L)	1.09±0.20	1.20±0.25	0.056
IgA/C3	2.77±0.75	4.45±1.21	<0.001
Recurrent mucosal infection [n (%)]	10 (14.3)	8 (40.0)	0.027
HBV infection [n (%)]	9 (13)	5 (25)	0.345

Abbreviations: BMI, Body mass index; RBC, red blood cell; HBV, hepatitis B virus.

Materials and methods

Ethics committee approval and patient consent

This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University and informed consent was obtained before study. This study has been performed in accordance with the principles of Declaration of Helsinki.

Patients

Our study included adult patients aged 14 years and over from The Sixth Affiliated Hospital of Sun Yat-sen University, in whom IgAN was diagnosed based on renal biopsy. Glomerular diseases listed below were excluded, secondary glomerular nephropathy, such as lupus nephritis, Henoch-Schonlein purpura nephritis, diabetic nephropathy, liver cirrhosis related IgAN and so forth.

Clinical definitions

The degree of proteinuria was defined as proteinuria ≥0.5 g/24 hr by quantifcation. Patients with eGFR <30 ml/min/1.73 m^2 were excluded from our study. Estimated glomerular fltration rate (eGFR)=175 × Scr (mg/dl)$^{-1.234}$ × age (year)$^{-0.179}$ [if female, × 0.79], MDRD equation [8]. Macrohematuria was defined as that gross hematuria recurred more than two times and urinalysis sustained abnormal in the interval. Hypertension was defined as resting systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or need for antihypertensive therapy. Body mass index (BMI) was calculated as the weight (in kilograms) divided by height squared (in square meters). The patients were divided into two groups based on the baseline serum IgA level (reference value, 0.7-4.0 g/L) which was measured by immunoturbidimetry (Orion Diagnosticn, Finland). Elevated or normal serum IgA was respectively defined as IgA >4.0 g/L or IgA ≤4.0 g/L. Recurrent mucosal infection was defined as the infections associated with mucosal tissues, such as nasitis, laryngopharyngitis and gastroenteritis are greater than or equal to 2 times per year within the first 3 years before initial diagnosis in our centre.

The treatment modalities included conservative therapy with angiotensin converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) agents and immunosuppressive therapy with immunosuppressive drugs (steroids or adding mycophenolate mofetil) based on ACEI/ARB.

Table 2. Pathological characteristics of IgA nephropathy patients with normal/elevated serum IgA

Variable	Normal IgA group n=59	Elevated IgA group n=16	*P*-value
Lee's grade [n (%)]			0.493
Grade II	5 (8.5)	0	
Grade III	26 (44.1)	7 (43.8)	
Grade IV	4 (35.6)	8 (50.0)	
Grade V	7 (11.9)	1 (6.3)	
Oxford classification			
M1 [n (%)]	47 (81.0)	8 (50.0)	0.028
E1 [n (%)]	17 (29.3)	3 (18.8)	0.600
S1 [n (%)]	23 (39.7)	4 (25.0)	0.281
Oxford T [n (%)]			0.366
T1	28 (48.3)	7 (43.8)	
T2	2 (3.4)	12 (12.5)	
Oxford C [n (%)]			0.415
C1	37 (63.8)	13 (81.3)	
C2	8 (13.8)	1 (6.3)	
IgG (+)	0 (0, 0)	0 (0, 0)	0.055
IgA (+)	3 (2, 3)	3 (2, 3)	0.670
IgM (+)	1 (1, 1)	1 (1, 1)	0.388

Abbreviations: Oxford M1, Mesangial score >0.5; Oxford E1, Endo capillary hypercellularity present; Oxford S1, Segmental glomerulosclerosis present; Oxford T, Tubular atrophy/interstitial fbrosis; T1, Tubular atrophy/interstitial fbrosis 26-50%; T2, Tubular atrophy/interstitial fbrosis >50%; Oxford C1, proportion of crescent <25%, Oxford C2, proportion of crescent >25%.

Pathological evaluation

Renal biopsies were processed for light and immunofluorescence microscopy which were reviewed by one pathologist who was unaware of clinical details of the patients.

The specimens were evaluated for the number of glomeruli, glomerulosclerosis, segmental sclerosis, proportion of crescents, Lee's grade, Oxford classification [8-11] and sediment strength of IgA.

Follow-up assessment

The follow-up ended after 15 months' clinical treatment as mentioned above. Evaluation of proteinuria remission was performed at 3, 6, 9, 12 and 15 months during follow-up period.

The primary outcome was the complete or partial remission of proteinuria. Complete remission of proteinuria was defined as a decrease in proteinuria to a level <0.3 g/24 h, inactive urine sediment test and normal serum albumin. Partial remission was defined as a reduction of proteinuria by at least 50% from baseline.

Statistical analysis

For quantitative variables, if symmetric distribution, mean ± standard deviation (SD) for statistical description, and Student's t test for statistical inference; and if asymmetric distribution, median (Q25-Q75) for description and Wilcoxon Rank Sum Test for inference. For qualitative variables, frequency for description and Chi-square test or Fisher's exact test for inference of the unordered categorical variables, and Wilcoxon Rank Sum Test for the ordinal ones.

The incidences of proteinuria remission were analyzed by Kaplan-Meier method and compared with the log rank test. Logistic regression model was used for multivariate analysis to identify the risk factors for proteinuria remission in IgAN. Cox proportional hazards regression model was used for multivariate analysis to identify the independent predictors of proteinuria remission. *P* values were two-sided and P<0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS statistical software (version 20.0).

Results

Clinical baseline data of enrolled patients

Our study included 181 adult patients (aged 14 years and over) from The Sixth Affiliated Hospital of Sun Yat-sen University, in whom 100 patients satisfied our proteinuria standard (proteinuria ≥0.5 g/24 hr). 10 patients were excluded from this study for less than 1 month's follow-up time. Elevated serum IgA level (serum IgA >4.0 g/L) was found in 20 (22.2%) patients out of the 90 eligible patients enrolled in our study. As shown in **Table 1**, serum antibody tests revealed that ratio of IgA/C3 and IgG level were increased significantly in elevated serum IgA group compared with normal IgA group (IgA/C3, 4.45±1.21 *vs.* 2.77±0.75 P< 0.001, serum IgG, 14.90±3.50 g/L *vs.* 10.27 ±3.49 g/L, P<0.001). There was also significant difference between the groups in recur-

Table 3. Treatment for IgA nephropathy patients with normal/elevated serum IgA

Variable	Normal IgA group n=50	Elevated IgA group n=18	*P*-value
Therapy			0.159
Steroids (Half dosage)	34 (68.0)	13 (72.2)	
1-3-5[a]	11 (22.0)	3 (16.7)	
1-2-3[b]	12 (24.0)	6 (33.3)	
Steroids (Adequate dosage)	7 (14.0)	0	
Steroids (Half dosage) +MMF	9 (18.0)	5 (27.8)	

Abbreviations: MMF, mycophenolate mofetil. [a]Steroids (500 mg/d) by venous transfusion during the first 3 days of the 1st, 3rd and 5th months after treatment. [b]Steroids (500 mg/d) by venous transfusion during the first 3 days of the 1st, 2nd and 3rd months after treatment.

Table 4. Proteinuria remission for IgA nephropathy patients with normal/elevated serum IgA

Variable	Normal IgA group n=70	Elevated IgA group n=20	*P*-value
Proteinuria remission			0.017
Complete remission	38 (54.3)	9 (42.4)	
Partial remission	17 (24.3)	10 (52.6)	
Time for remission	6 (2, 8.25)	2.5 (2, 4.75)	0.040

rent mucosae infection rate (40% *vs.* 14.3% in normal IgA group, P=0.027). No differences were found between the two groups regarding the patients' gender, age, body mass index, blood pressure, protein uria quantitation, serum creatinine/blood urea nitrogen.

Pathological characteristics of renal biopsies

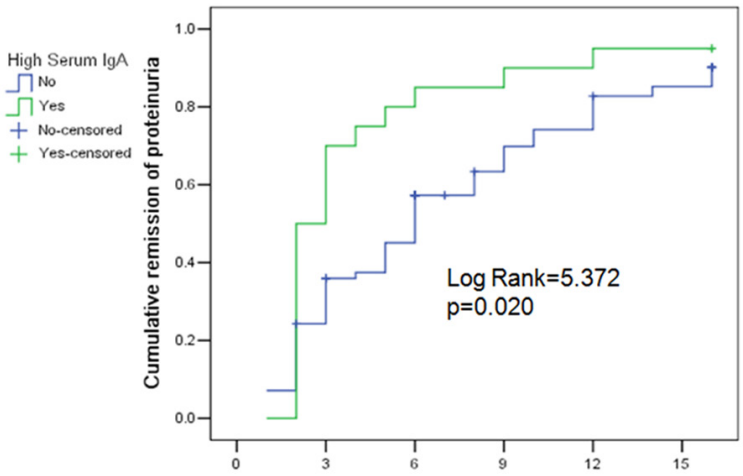
Kidney biopsy was performed for 75 (16 patients from elevated serum IgA group) patients in our centre (15 patients were ruled out for unavailable pathological sections). Histologic results showed that mesangial proliferation (M1) was obviously more common in normal IgA group compared with elevated serum IgA group (81% *vs.* 50%, P=0.028). The rates of endo capillary hypercellularity (E1) and segmental sclerosis (S1) in normal IgA group were more higher than that in elevated IgA group (E1, 29.3% *vs.* 18.8% in elevated serum IgA group, P=0.600, S1, 39.7% *vs.* 25.0% in elevated serum IgA group, P=0.281). Incidence of crescent was more common in elevated IgA group compared with normal IgA group (C1+C2, 87.6% *vs.* 77.6% in normal IgA group, P=0.383), while the proportion of crescent less than 25% (C1) more often occurred in elevated IgA group (81.3% *vs.* 63.8% in normal IgA group). Global glomerulosclerosis, tubular atrophy/interstitial fibrosis, mesengial IgA deposits, Lee's grade and podocyte lesion did not differ between the groups (**Table 2**).

Treatment and outcome of enrolled patients

Conservative therapy (ACEI or ARB agents) was applied to 22 patients in which 2 (10%) and 20 (28.6%) patients were from elevated/normal IgA groups respectively (P=0.159). Steroids therapy was used in 68 patients in which 18 (90%) and 50 (71.4%) patients were from elevated/normal IgA groups respectively (P=0.159).

In elevated IgA group, 13 (72.2%) patients took half dosage (0.5 mg/Kg/d) of steroids for oral administration, in which 9 patients received steroids pulse treatment synergistically (3 patients received steroids 500 mg/d by venous transfusion during the first 3 days of the 1st, 3rd and 5th months after treatment, 6 patients received steroids 500 mg/d by venous transfusion during the first 3 days of the 1st, 2nd and 3rd months after treatment). The remaining 5 (27.8%) patients were treated with half dosage of steroids plus mycophenolate mofetil (MMF, 500 mg b.i.d) for oral administration. In normal IgA group, 34 (68%) patients took half dosage of steroids for oral administration, in which 23 patients received steroids pulse treatment synergistically (11 patients received steroids 500 mg/d by venous transfusion during the first 3 days of the 1st, 3rd and 5th months after treatment, 12 patients received steroids 500 mg/d by venous transfusion during the first 3 days of the 1st, 2nd and 3rd months after treatment). 7 (14%) patients received adequate dosage of steroids (1.0 mg/Kg/d) for oral administration. 9 (18%) patients were treated with half dosage of steroids plus MMF (500 mg b.i.d) for oral administration (**Table 3**).

At the end of follow-up time, 74 (82.2%)IgAN patients achieved proteinuria remission with the median remission time 5 months (range 2-8 months). As shown in **Table 4**, the protein-



No. at risk						
Total	90	62	40	20	14	7
High Serum IgA	20	10	4	3	2	1
Normal Serun IgA	70	52	36	17	12	6

Follow-up remission of proteinuia(%)

Time	3M	6M	9M	12M	15M
Total(90)	53	69	78	88	93
High Serum IgA(20)	80	85	90	95	95
Normal Serum IgA(70)	45	64	75	86	93

Figure 1. Cumulative proteinuria remission rate for patients with or without high serum IgA seen in follow-up.

uria remission rate for elevated serum IgA group was higher than the normal IgA group (95% *vs.* 78.6%, P=0.079). There was a remarkably shorter median remission time in elevated IgA group (2.5 months *vs.* 6 months for normal IgA group, P=0.040). The proportions of complete/partial remission in elevated/normal IgA group were 45.0% *vs.* 54.3% and 50.0% *vs.* 24.3% (P=0.017) (**Table 4**).

The correlation between baseline serum IgA level and proteinuria remission

Kaplan-Meier curves showed that proteinuria remission rate for IgAN patients with high serum IgA was 80%, 85%, 90%, 95% and 95% after 3, 6, 9, 12 and 15 months respectively compared with patients with normal serum IgA (proteinuria remission rate, 45%, 64%, 75%, 86% and 93%, P=0.020) (**Figure 1**).

Cox proportional hazards regression model indicated that elevated serum IgA (RR=1.984, P=0.040) and steroids therapy (RR=2.192, P=0.030) were independent predictors for proteinuria remission in IgAN patients after adjusting for potential risk factors, such as age, segmental sclerosis (**Table 5**).

Discussion

Elevated serum IgA level occurred in 22.2% of IgAN patients in our centre, which was obviously lower than 50%-70% [6]. In the present study, normal serum IgA was regulated within 0.7-4.0 g/L by immunoturbidimetry according to our clinical laboratory, while 315-350 mg/dL was often used to define elevated serum IgA in previous studies [7, 12]. Thus, our reference range (serum IgA >4.0 g/L) reduced the diagnosis sensitivity to some extent for elevated serum IgA in IgAN patients.

Previous study had shown that higher serum IgA and C3 levels were closely related to IgAN [13]. Saito K indicated that measurement of serum IgA and C3 might predict the diagnosis of patients with IgAN prior to renal biopsy [7]. Madea suggested that elevated serum IgA (IgA >315 mg/dl) and serum IgA/C3 ratio (IgA/C3 >3.01) appeared to reflect the histological severity of IgAN and could serve as a marker of the IgAN progression [13].

Different studies have shown that IgA1 and IgA2 are two subtypes of IgA [14, 15]. It is believed that IgAN is a form of glomerulonephritis with predominant deposition of abnormally glycosylated polymerise IgA1 (pIgA1) [14, 15]. Sever MS and coworkers implied that elevated serum IgA1 was associated with recurrent IgAN in patients received renal transplants [16]. Nevertheless, in clinical practice, serum IgA detection plays a referential role in assisted diagnosis of IgAN especially for patients who refuse invasive renal biopsy, which inspires us to probe into the relationships between increased serum IgA with clinical features, renal pathology and treatment outcomes of IgAN.

Table 5. Risk factors for proteinuria remission in IgA nephropathy patients

Variable	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Age (per 1 year)	0.977 (0.955-0.999)	0.044	0.985 (0.961-1.010)	0.245
Elevated IgA (Yes:No)	1.700 (1.002-2.884)	0.202	1.984 (1.031-3.815)	0.040
S1 (Yes:No)	0.553 (0.318-0.960)	0.035	0.616 (0.342-1.110)	0.107
HBV infection (Yes:No)	0.464 (0.228-0.943)	0.034	0.522 (0.220-1.240)	0.141
Steroids (Yes:No)	2.394 (1.341-4.274)	0.003	2.192 (1.077-4.463)	0.030

Abbreviations: S1, Segmental glomeruloscleosis present according to Oxford classification; HBV, hepatitis B virus.

In present study, clinical data of enrolled patients showed that IgA/C3 ratio was increased significantly in elevated serum IgA group, which was consistent with previous manuscript [13]. Additionally, Wyatt RJ reported that co-deposition of IgG and pIgA1 was found in the mesangium of IgAN pediatric [17]. Our results indicated that significantly increased serum IgG was detected in IgAN patients with elevated serum IgA. The association between increased serum IgG and deposition of aberrantly glycosylated pIgA1 in IgAN needs to be elucidated further. The reason for significant difference between the groups in recurrent mucosae infection rate may be resulted from increased serum IgG in elevated serum IgA group.

Roszkowska-Blaim M provided evidence that elevated serum IgA at baseline might be associated with mesangial proliferation and segmental sclerosis, but had no effect on the presence of proteinuria or on the worsening of kidney function in children with IgAN [18]. However, our results indicated that mesangial proliferation, endocapillary hypercellularity and segmental sclerosis were more common in normal IgA group compared with elevated IgA group in adult IgAN patients. Furthermore, the proteinuria remission rate for elevated serum IgA group was higher than the normal IgA group within a remarkably shorter median remission period. It should be noted that although the difference for proportions of steroids therapy was insignificant between groups, a higher ratio of steroids therapy was adopted in elevated IgA group (90% *vs.* 71.4%, P=0.159). With respect to therapeutic schemes, modified Pozzi method (steroids 500 mg/d by venous transfusion during the first 3 days of the 1st, 2nd and 3rd months after treatment) was applied in 33.3% of patients with elevated IgA, which was more common than that of normal IgA group (24%).

Furthermore, it is worth noting that crescents were more common in elevated IgA group (C1+C2, 87.6% *vs.* 77.6% in normal IgA group). Meanwhile, the proportion of crescent less than 25% (C1) more often occurred in elevated IgA group (81.3% *vs.* 63.8% in normal IgA group), which was probably related to increased rate of recurrent mucosae infection in high IgA group. It is believed that activity indicators, such as crescent, necrosis lesions and microthrombosis tend to become chronic pathological lesions after about 3 months, which facilitates the progression of IgAN from acute kidney injuries to chronic kidney diseases [19]. Recently, the crescent score was introduced as a new indicator to predict renal prognosis of IgA nephropathy by Oxford classification which provided the strong evidence that even proportion of crescent less than 25% (C1) predicted an adverse events [20]. In view of the differences in steroids pulse treatment and crescent score between groups, we conclude that steroids pulse treatment, such as modified Pozzi method, probably could improve the prognosis of IgAN, which is being verified in our randomized controlled trial. Based on adjusting the variable of steroids therapy, elevated serum IgA was still related to proteinuria remission in IgAN patients (**Table 5**). In view of the data as mentioned previously, earlier intervention for IgAN with elevated serum IgA may achieve better clinical outcomes.

This study was an observational study and was limited by its small sample size. A randomized controlled study with long-term follow-up is necessary. In addition, correlations between certain IgA subtype, such as serum IgA1, clinicopathological features and renal outcomes in IgAN patients are required to be further elucidated.

In summary, the elevated serum IgA was found in 20 (22.2%) IgAN patients in our centre. In elevated IgA group, mesangial proliferation was less prominent, whereas the proportion of crescent less than 25% (C1) was more common compared with normal IgA group. Therefore, earlier intervention for IgAN with elevated serum IgA may achieve better clinical outcomes. Cox proportional hazard regression model indicated that elevated serum IgA and steroids therapy were independent predictors for proteinuria remission in IgAN patients, which suggested that elevated serum IgA might predict earlier proteinuria remission in IgAN patients.

Acknowledgements

This study was supported by the Nature Science Foundation of China (NO.81470953).

Disclosure of conflict of interest

None.

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