Relationship between serum C3/C4 ratio and prognosis of immunoglobulin A nephropathy based on propensity score matching

Yan Zhang, Shu-Wei Duan, Pu Chen, Zhong Yin, Yong Wang, Guang-Yan Cai, Xiang-Mei Chen

Department of Nephrology, Chinese People's Liberation Army General Hospital, Chinese People's Liberation Army Institute of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Disease Research, Beijing 100853, China.

Abstract

Background: Aberrant activation of the complement system plays an important role in the pathogenesis and development of immunoglobulin A nephropathy (IgAN). The relationship between serum complement and the clinical-histopathological features and outcomes of IgAN is controversial. This retrospective study aimed to examine the relationship between the complement 3/4 (C3/C4) ratio and the clinicopathologic changes and prognosis of patients with IgAN.

Methods: A total of 397 patients with primary IgAN from January 2007 to December 2012 at the Chinese People's Liberation Army General Hospital were included in this study. The correlation test and Chi-square test or one-way analysis of variance test were performed to evaluate the relationship between the C3/C4 ratio and other clinical-pathological factors. Propensity score matching and a multivariate Cox regression model were used to calculate the risk factors of renal outcome.

Results: The median follow-up period was 75 months. During the follow-up period, 62 patients (15.6%) developed into the end-stage renal disease (ESRD). The C3/C4 ratio at baseline was associated with the level of serum creatinine (SCr), 24 h urinary protein excretion (24 h Upre), global glomerular sclerosis, and tubulointerstitial lesion. The level of SCr and 24 h Upre and the degree of chronic kidney injury were statistically different among groups defined by different C3/C4 ratio levels. The survival rates of patients among groups with different C3/C4 ratio levels were different. After propensity score matching, eighty-eight pairs of patients were successfully matched, and the C3/C4 ratio was an influencing factor for the patients' outcome (hazard ratio 0.587, 95% confidence interval 0.329–0.880). Patients with a C3/C4 ratio <3.6 had a poorer outcome compared with the others ($P = 0.002$).

Conclusions: IgAN patients with decreased C3/C4 ratio displayed significantly more severe clinical symptoms and chronic renal injury than patients with higher ratios. A low C3/C4 ratio could be a risk factor for patients developing to ESRD.

Keywords: Complement; Serum C3/C4; Immunoglobulin A nephropathy; Prognosis

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a leading cause of the end-stage renal disease (ESRD).[1] The outcomes of IgAN are highly variable among individuals. Several clinical risk factors for the disease progression have been confirmed, such as renal function, hypertension, proteinuria, hyperuricemia, and episodes of macroscopic hematuria.[2-5]

IgAN is considered to be an autoimmune disease.[6] Several studies have confirmed that the complement system is abnormally activated, mostly through the recognition molecule mannose-binding lectin (MBL) and the alternative pathway, and it plays a key role in the occurrence and development of IgAN.[7] Although serum complement levels are at a normal range in patients with IgAN, they are markers of the degree of complement activation.[8]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000674

Predicting the prognosis of IgAN by serum complements has been a research hotspot, but some main issues remain controversial. Several studies confirmed that the complement 3 (C3) and complement 4 (C4) levels could affect the outcomes of IgAN.[9,10] In contrast, our center's previous study showed that serum C3 levels in IgAN did not play a key role in renal progression.[11] Interestingly, a new study of Pan *et al*[12] demonstrated that the C3/C4 ratio may be superior to C3 or C4 alone in predicting the prognosis of IgAN patients.

In this study, we focus on the relationship between the C3/C4 ratio and clinical-pathological changes, and its value to forecast the renal outcomes of IgAN.

Methods

Ethical approval

This retrospective study was approved by the local ethics committee of the People's Liberation Army (PLA) General

Correspondence to: Xiang-Mei Chen, Department of Nephrology, Chinese People's Liberation Army General Hospital, Beijing 100853, China
E-Mail: xmchen301@126.com

Chinese Medical Journal 2020;133(6)

Received: 26-09-2019 **Edited by:** Yuan-Yuan Ji

Hospital (No. S2018-246-01) and was exempted from informed consent from patients.

Subjects

Patients with biopsy-proven IgAN from January 2007 to December 2012 at the Chinese PLA General Hospital were included. All of them were more than 18 years old. Patients who had the following situations were excluded: (1) secondary cause of IgAN, such as systemic lupus erythematosus, Henoch-Schonlein purpura, or hepatic diseases; (2) combined with other glomerular diseases, such as membranous nephropathy; (3) less than eight glomeruli in renal biopsy specimens; (4) combined with other systemic diseases or connective tissue diseases; (5) the estimated glomerular filtration rate (eGFR) was <15 ml·min^{-1}·1.73 m^{-2} at the time of renal biopsy; (6) gestation or perinatal period at the time of renal biopsy; (7) death from non-renal causes in 5 years; (8) abnormal liver function, defined as twice of the high normal range of glutamic-pyruvic transaminase (GPT) or glutamic oxalacetic transaminase (GOT); (9) immunosuppressive therapy in the last 6 months before renal biopsy; (10) baseline or follow-up data was incomplete; and (11) less than 12 months of follow-up. Finally, 397 patients were successfully included.

Clinical measures

Clinical data were recorded at biopsy, including gender, age, mean arterial pressure (MAP), 24-h urinary protein excretion (24 h Upre), GOT, GPT, serum albumin (ALB), serum creatinine (Scr), uric acid (UA), total cholesterol, triglyceride, hemoglobin (Hb), serum IgA, IgG, C3, and C4 levels. All patients were divided into two groups according to the cut-off point of the first quartile of all C3/C4 ratios. One-hundred patients were included in the group 1, with a C3/C4 ratio less than 3.6. The other 297 patients were included in the group 2. In addition, treatment with prednisone, immunosuppressant and/or angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker was recorded after IgAN was diagnosed. The chronic kidney disease (CKD)-epidemiology collaboration equation was used to calculate the patients' eGFR.[13]

Histopathological data

The following components were evaluated: global glomerular sclerosis (G), mesangial proliferation (M), endocapillary hypercellularity (E), segmental sclerosis/adhesions (S), tubularatrophy/interstitial fibrosis (T), and crescents (C). G0, G1, G2, G3, and G4 reflect global glomerular sclerosis involving 0, <10%, 10%≤ G <25%, 25%≤ G <50%, and ≥50% of glomeruli, respectively; the presence of 50% of glomeruli showing mesangial hypercellularity is denoted as M1, whereas less than 50% glomeruli are classified as M0; E1 is defined as any endocapillary hypercellularity; S1 indicates any segmental glomerulosclerosis; and T0, T1, and T2 reflect tubularatrophy/interstitial fibrosis involving 0% to 25%, 26% to 50%, or >50% of the cortical area, respectively; C0, C1, and C2 denote no cellular or fibrocellular crescents, cellular/fibrocellular crescents in <25% of glomeruli, and crescents in ≥25% of glomeruli, respectively.[1]

Follow-up and primary outcome

As a retrospective study, we collected all the medical information of the patients in our hospital and called the patient at the end of the follow-up to obtain the latest test results. The endpoint of this study was defined as evolving into ESRD. Twenty-nine patients (7.3%) were lost to follow-up during the second year, 48 patients (12.1%) during the third year, and 75 patients (18.9%) during the fifth year.

Calculation of sample size

According to clinical experience, it was assumed that the risk factors of progression maybe 10 to 15. The sample size was 10 to 20 times the number of the independent variables, and thus the observed number should be 100 to 300 cases. Considering the rate of the lost to follow-up, we needed about 110 to 330 patients.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 (International Business Machines Corporation, IBM, USA). Normally distributed continuous data were expressed as mean ± standard deviation, non-normally distributed data were recorded as median with interquartile ranges, and categorical variables were presented as counts with percentages. *T* test or Mann-Whitney *U* test was used to test the differences between two groups. Intergroup differences were compared using the Chi-square test for categorical variables, one-way analysis of variance test for normally distributed continuous data, and Kruskal-Wallis test for non-normally distributed data. Pearson or Spearman correlation tests were performed to evaluate the relationship between two indexes. A multivariate Cox regression model was used to calculate the risk factors of renal outcome. The log-rank test was used to compare Kaplan-Meier curves. In addition, patients were assigned a 1: 1 propensity score matching (PS matching) by using the PS matching extension program in SPSS 23.0 with the C3/C4 ratio <3.6 as the dependent variable. $P<0.05$ was considered a significant difference.

Results

Baseline characteristics and correlation analysis

Three hundred and ninety-seven patients with the median age of 35 [14] years were enrolled in the study. The median follow-up period was 75 [43] months. The clinical features and histopathological characteristics of the included patients at the time of renal biopsy are shown in Table 1. Of these patients, 217 (54.7%) were male, 77 patients (19.4%) had decreased C3 levels, and only 17 patients (4.3%) presented increased C4. The rates of M1, E1, S1, T1 + 2, C1 + 2, and G3 + 4 were 49.4%, 2.3%, 45.3%, 47.3%, 21.9%, and 40.6%, respectively. Sixty-two patients (15.6%) progressed to ESRD during the follow-up period. The C3/C4 ratio was positively correlated with eGFR, IgG,

Table 1: Baseline characteristics of patients with biopsy-proven IgAN and the relationship between clinical-pathological items and the C3/C4 ratio ($N = 397$).

Characteristics	Values	C3/C4 ratio	
		r	*P*
Male	217 (54.7)	0.090	0.074
Age (years)	35 [14]	−0.025	0.395
eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	82.8 [49.6]	0.256	<0.001
CKD stages		−0.224	<0.001
Stage 1	173 (43.6)		
Stage 2	106 (26.7)		
Stage 3	92 (23.2)		
Stage 4	26 (6.5)		
Hypertension	197 (47.9)	−0.119	0.016
Low complement 3	77 (19.7)		
High complement 4	17 (4.1)		
G		−0.135	0.007
G0	65 (16.4)		
G1	72 (18.2)		
G2	98 (24.7)		
G3	88 (22.2)		
G4	73 (18.4)		
M1	196 (49.4)	−0.035	0.484
E1	9 (2.3)	0.019	0.708
S1	180 (45.3)	0.063	0.209
C		−0.070	0.165
C0	310 (78.1)		
C1	73 (18.4)		
C2	14 (3.5)		
T		−0.162	0.001
T0	209 (52.6)		
T1	95 (23.9)		
T2	93 (23.4)		
C3 deposition	311 (78.3)	0.050	0.316
IgG deposition	108 (27.2)	−0.014	0.785
Follow-up period (months)	75 [43]	0.108	0.032
MAP (mmHg)	96.7 [16.7]	−0.106	0.035
Serum IgA (mg/dL)	291.5 [131.5]	−0.012	0.812
Serum IgG (mg/dL)	1050 [380]	0.141	0.005
C3 (mg/dL)	107.0 [27.1]	0.161	0.001
C4 (mg/dL)	25.0 [9.5]	−0.759	<0.001
Hb (g/L)	133.3 ± 20.2	0.103	0.041
Scr (μmol//L)	94.5 [54.8]	−0.251	<0.001
UA (μmol//L)	368.2 [145.7]	−0.158	0.002
Alb (g//L)	39.7 [6.0]	0.163	0.001
GOT (U/L)	16.2 [5.9]	0.145	0.004
GPT (U/L)	16.1 [11.0]	0.017	0.743
TG (mmol//L)	1.5 [1.1]	−0.086	0.094
TC (mmol//L)	4.6 ± 1.3	−0.032	0.534
24 h Upre (g/24 h)	1.3 [1.9]	−0.142	0.005
Therapy			
ARB/ACEI	299 (75.3)	0.092	0.068
Prednisone	151 (38.0)	−0.027	0.598
Immunosuppressant	91 (22.9)	−0.031	0.541
ESRD	62 (15.6)	−0.185	<0.001

Values were shown as *n* (%), mean ± standard deviation, or median [IQR]. IgAN: Immunoglobulin A nephropathy; eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; G: Global glomerular sclerosis; M: Mesangial proliferation; E: Endocapillary hypercellularity; S: Segmental sclerosis/adhesions; C: Crescents; T: Tubularatrophy/interstitial fibrosis; MAP: Mean arterial pressure; C3: Complement 3; C4: Complement 4; 24 h Upre: 24-hour urinary protein excretion; Hb: Hemoglobin; Scr: Serum creatinine; UA: Uric acid; Alb: Serum albumin; GOT: Glutamic oxalacetic transaminase; GPT: Glutamic-pyruvic transaminase; TG: Triglyceride; TC: Total cholesterol; ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; ESRD: End-stage renal disease; IQR: Interquartile range.

Table 2: Clinical characteristics or histopathological features of IgAN patients among the four groups with distinct C3/C4 ratios ($N = 397$).

Items	C3/C4 ratio <3.6 ($n = 100$)	3.6≤ C3/C4 ratio <4.2 ($n = 97$)	4.2≤ C3/C4 ratio <5.1 ($n = 101$)	C3/C4 ratio ≥5.1 ($n = 99$)	χ^2	*P*
Male	56 (56.0)	57 (58.8)	60 (59.4)	44 (44.4)	5.227	0.121
Age (years)	34 [14]	40 [13]*	33 [15]	35 [13]	2.754	0.097
MAP (mmHg)	98.3 [19.5]	96.7 [16.7]	93.3 [20.0]	93.3 [16.5]	2.600	0.107
eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	66.9 [47.8]	81.5 [49.4]	86.7 [48.1]*	94.3 [43.9]*	14.693	<0.001
SCr (μmol/L)	104.9 [84.1]	92.3 [54.3]*	92.0 [51.5]*	81.8 [45.0]*	14.392	<0.001
UA (μmol/L)	411.1 ± 114.7	367.3 ± 89.5*	384.4 ± 104.7	353.9 ± 110.3*	11.363	0.001
24 h Upre (g)	1.8 [2.8]	1.3 [1.8]*	1.2 [1.6]*	1.0 [1.2]*	10.271	0.016
G					7.737	0.056
Mild	49 (49.0)	62 (63.9)	58 (58.0)	66 (66.7)		
Severe	51 (51.0)	35 (36.1)	42 (42.0)	33 (33.3)		
T					17.469	0.023
None	41 (41.0)	51 (52.6)	55 (54.5)	62 (62.6)		
T lesion	59 (59.0)	46 (47.4)	46 (45.5)	37 (37.4)		
ESRD	28 (28.0)	13 (13.4)	12 (11.9)	9 (9.1)	16.535	0.001

Values were shown as *n* (%), mean ± standard deviation, or median [IQR]. *Compared with the C3/C4 ratio <3.6 group, *P* was less than 0.05. The degree of G was divided into two levels according to the G score, mild: G0 + 1 + 2, severe: G3 + 4; the degree of T was divided into two levels according to the T score, none: T0, T lesion: T1 + 2. IgAN: Immunoglobulin A nephropathy; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate; SCr: Serum creatinine; UA: Uric acid; 24 h Upre: 24-hour urinary protein excretion; G: Global glomerular sclerosis; T: Tubularatrophy/interstitial fibrosis; ESRD: End-stage renal disease; IQR: Interquartile range.

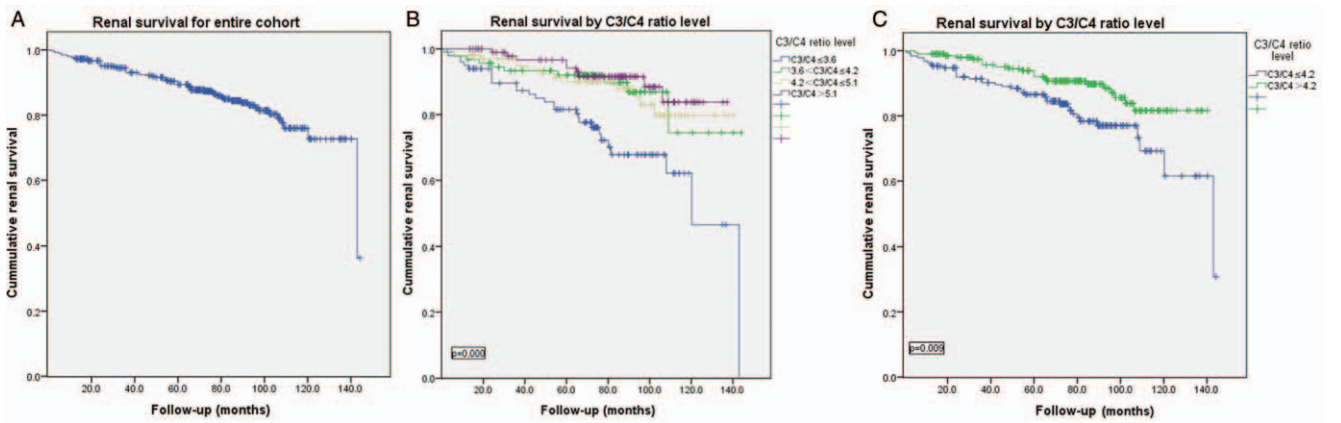

Figure 1: Probabilities of event-free survival. (A) In the entire cohort, the probability of event-free survival was 97.5% at 1 year, 89.2% at 5 years, and 70.3% at 10 years. (B) At 10 years, the probability of event-free survival was 46.4%, 60.7%, 81.5%, and 83.7% for patients with a C3/C4 ratio ≤3.6, 3.6<C3/C4 ratio≤4.2, 4.2<C3/C4 ratio≤5.1, and C3/C4 ratio >5.1, respectively. (C) In patients with a C3/C4 ratio ≤4.2, the probability of event-free survival at 10 years was 55.3%.

Hb, ALB, and GOT, and negatively correlated with G, T, MAP, SCr, UA, 24 h Upre, and outcome [Table 1].

Relationship between distinct C3/C4 ratios and clinical characteristics or histopathological features

We divided all patients into four groups according to the quartiles of the C3/C4 ratio. Among the four groups, the eGFR, SCr, UA, and 24 h Upre were statistically different. The rates of a T lesion and severe G among the four groups were different. The rate of ESRD during the follow-up period was also statistically different [Table 2]. The lower the C3/C4 ratio is, the higher the SCr and 24 h Upre are, the more severe the chronic renal injury became, and the poorer the outcomes are.

Kaplan-Meier survival analysis indicated that the probabilities of event-free survival were significantly different among the groups with different levels of C3/C4 ratio [Figure 1]. The event-free survival for the entire cohort was 97.5% at 1 year, 89.2% at 5 years, and 70.3% at 10 years [Figure 1A]. However, when all patients were divided into the four groups according to the quartile of the C3/C4 ratio, the probabilities of event-free survival in patients with a C3/C4 ratio <3.6 were 95.0% at 1 year, 81.6% at 5 years, and 46.4% at 10 years. The event-free survival was 96.9% at 1 year, 89.3% at 5 years, and 60.7% at 10 years for patients with the C3/C4 ratio ranging from 3.6 to 4.2. In patients with a 4.2≤ C3/C4 ratio <5.1, the event-free survival was 97.0% at 1 year, 89.7% at 5 years, and 81.5% at 10 years. In patients with C3/C4 ratio ≥5.1, the event-free survival was 100% at 1 year, 91.5% at 5 years, and 83.7% at 10 years [Figure 1B].

Outcomes and C3/C4 ratio

Univariate and multivariate Cox proportional hazard regression indicated that the C3/C4 ratio, 24 h Upre, SCr,

Table 3: Univariate and multivariate Cox proportional hazard regression analyses of the predictors of outcome in patients with IgAN.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
C3/C4 ratio	0.700 (0.561–0.874)	0.002	0.922 (0.731–1.164)	0.496
24 h Upre	1.305 (1.192–1.428)	<0.001	1.226 (1.103–1.362)	<0.001
SCr	1.013 (1.011–1.015)	<0.001	1.008 (1.005–1.011)	<0.001
G	3.007 (2.234–4.048)	<0.001	1.859 (1.304–2.649)	0.001
T	3.684 (2.611–5.197)	<0.001	1.289 (0.811–2.048)	0.283

IgAN: Immunoglobulin A nephropathy; HR: Hazard ratio; CI: Confidence interval; 24 h Upre: 24-hour urinary protein excretion; Scr: Serum creatinine; G: Global glomerular sclerosis; T: Tubularatrophy/interstitial fibrosis.

Table 4: Clinical and pathological features of IgAN patients in two groups divided by the cut-off value of C3/C4 ratios before and after PS matching.

Items	Before PS matching				After PS matching			
	C3/C4 <3.6 (*n* = 98)	C3/C4 ≥3.6 (*n* = 299)	χ^2 or *Z*	*P*	C3/C4 <3.6 (*n* = 88)	C3/C4 ≥3.6 (*n* = 88)	χ^2 or *Z*	*P*
T1 + 2	58 (59.2)	130 (43.5)	7.303*	0.007	50 (56.8)	40 (45.5)	2.274*	0.132
G3 + 4	50 (51.0)	111 (37.1)	5.978*	0.016	43 (48.9)	31 (35.2)	3.358*	0.067
SCr (μmol/L)	105.3 [84.4]	88.5 [50.0]	−3.597†	<0.001	101.9 [60.2]	94.4 [58.3]	−1.555†	0.120
24 h Upre (g)	1.7 [2.8]	1.1 [1.5]	−2.979†	0.004	1.7 [2.5]	1.3 [1.5]	−1.457†	0.145
Follow-up time (months)	72.3 [50.5]	77.0 [41.2]	−1.88†	0.060	73.1 [43.2]	80.0 [33.3]	−1.311†	0.190
ESRD	28 (28.6)	34 (11.4)	16.570*	<0.001	22 (25.0)	6 (6.8)	10.873*	0.001
Corticosteroids	39 (39.8)	112 (37.5)	0.171*	0.679	33 (37.5)	32 (36.4)	0.024*	0.876

Values were shown as *n* (%), or median [IQR]. *χ^2 values. †*Z* values. IgAN: Immunoglobulin A nephropathy; PS matching: Propensity score matching; T: Tubularatrophy/interstitial fibrosis; G: Global glomerular sclerosis; Scr: Serum creatinine; 24 h Upre: 24-hour urinary protein excretion; ESRD: End-stage renal disease; IQR: Interquartile range.

and G and T lesion were factors affecting the prognosis of IgAN, with the respective unadjusted hazard ratio (HR): 0.700 (95% confidence interval [CI] 0.561–0.873, $P = 0.002$), 1.305 (95% CI 1.192–1.428, $P<0.001$), 1.013 (95% CI 1.011–1.015, $P<0.001$), 3.007 (95% CI 2.234–4.048, $P<0.001$), and 3.684 (95% CI 2.611–5.197, $P<0.001$). After multivariate adjustment, only 24 h Upre (HR 1.226 [95% CI 1.103–1.362], $P<0.001$), SCr (HR 1.008 [95% CI 1.005–1.011], $P<0.001$), and G (HR 1.859 [95% CI 1.304–2.649], $P = 0.001$) were identified as independent predictors of outcome in our cohort of IgAN patients [Table 3].

Effect of C3/C4 ratio on the outcome of IgAN based on PS matching

We divided all patients into two groups according to the cut-off point of the first quartile of all C3/C4 ratios. There were statistical differences for the T lesion, G score, SCr, and 24 h Upre between group 1 and group 2 [Table 4]. During the follow-up, there were 28 patients (28.6%) in group 1 who progressed to ESRD and 34 patients (11.4%) in group 2, and this difference was statistically significant ($P<0.001$). Kaplan-Meier survival analysis indicated that the survival rate of the renal outcome was significantly different between the two groups [Figure 2A] ($P<0.001$). Then we performed a PS matching, and 88 pairs of patients were successfully matched. After PS matching, the differences for 24 h Upre, SCr, and T and G lesion between the two groups disappeared [Table 4]. The incidence rates of ESRD were 25.0% (22 patients) in group 1 and 6.8% (six patients) in group 2. After PS matching, the renal outcomes for the two groups were still different [Figure 2B] ($P = 0.002$). Multivariate Cox proportional hazard regression analyses indicated that the SCr, C3/C4 ratio, 24 h Upre, G lesion, and corticosteroids therapy were risk factors for the outcome of IgAN [Table 5].

Discussion

Since its initial description in 1968 by Berger and Hinglais,[14] IgAN has become the most common primary glomerular disease, and up to 45% of glomerular diseases are IgAN.[11,15,16] IgAN is characterized by IgA or IgA-based deposition in the glomerular mesangial area. The clinical manifestations of IgAN are extremely variable, ranging from asymptomatic proteinuria and/ or hematuria to rapidly progressive renal failure. IgAN is a slowly progressive disease, and 30% to 50% of patients eventually progress to ESRD within 20 to 30 years after their initial diagnosis.[4,17] In this retrospective study, we enrolled 397 primary IgAN patients. During the period with a mean of 73.4 months' follow-up period, 15.6% of the included patients progressed to ESRD.

The pathogenesis of IgAN includes several steps, namely: (1) the generation of aberrant glycosylation of IgA1, (2) specific antibodies binding to the galactose-deficient IgA1, and (3) the formation of immune complexes deposits in the

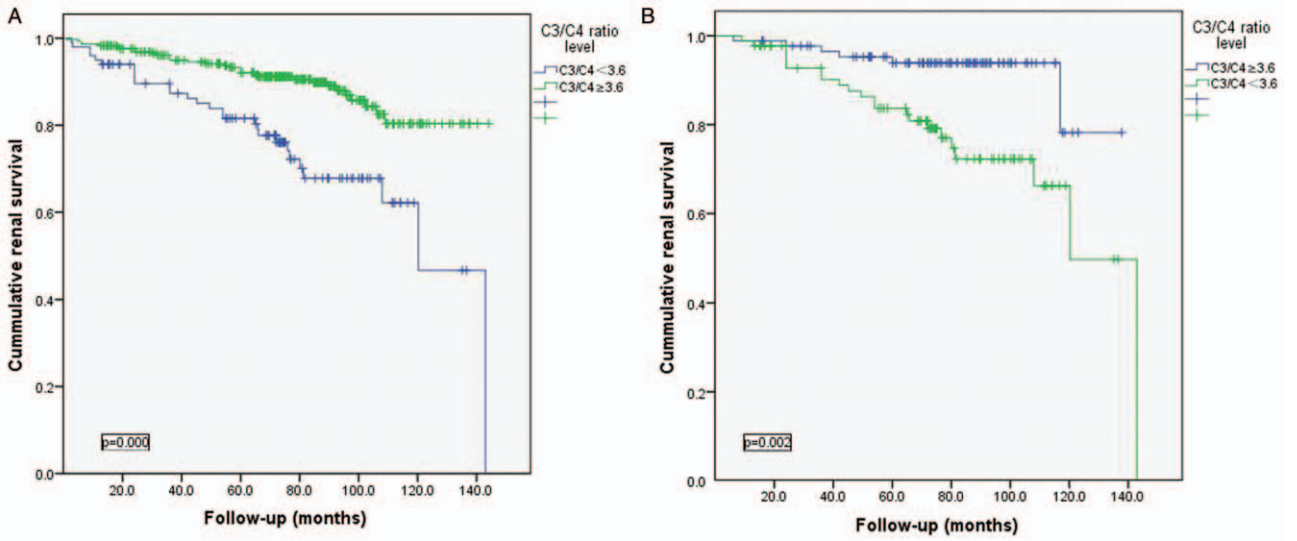

Figure 2: Kaplan-Meier survival based on the C3/C4 ratio before (A) and after PS matching (B). The probability of event-free survival between the two groups (group 1: C3/C4 ≤3.6, group 2: C3/C4 >3.6) was different before and after PS matching. PS matching: Propensity score matching.

Table 5: Influence factors for prognosis of IgAN based on PS matching.

Items	*P*	Exp (B)	95% CI of Exp (B)
C3/C4 ratio	0.010	0.587	0.328–0.880
SCr	<0.001	1.011	1.005–1.016
24 h Upre	0.001	1.341	1.129–1.593
G	0.035	1.560	1.032–2.358
Corticosteroids	0.001	0.212	0.081–0.551

IgAN: Immunoglobulin A nephropathy; PS matching: Propensity score matching; CI: Confidence interval; Scr: Serum creatinine; 24 h Upre: 24-hour urinary protein excretion; G: Global glomerular sclerosis.

glomerular mesangium, activating mesangial cells and leading to glomerular damage.[18] Meanwhile, complement is aberrantly activated by both the alternative and MBL pathways, which could amplify the inflammatory response and aggravate the kidney injury. Komatsu *et al*[19] showed that the serum C3 level was lower in patients with severe IgAN compared with non-IgAN. However, these patients with low C4 levels exhibited better renal presentations at baseline, which might be associated with a poor prognosis. Activated C3 was associated with increased proteinuria.[8] Furthermore, C3 hypocomplementemia and mesangial C3 deposition are independent risk factors of a doubling of the baseline serum creatinine (D-SCr) of IgAN.[9] In IgAN patients, Pan *et al*[10] found that the serum C4 levels were either significantly associated with the segmental sclerosis/adhesions, tubularatrophy/interstitial fibrosis, and Crescents of the Oxford classification or with eGFR values. In their study, they proposed the eGFR decline of more than 30% as the primary outcome and demonstrated that increased C4, as well as decreased C3, was significantly associated with the primary outcome. Lbels *et al*[20] suggested that the serum C4 level has an independent association with patient outcomes, as it was related to the severity of chronic inflammation. Zhu *et al*[21] found that serum C4 concentrations at the time of renal biopsy were associated with eGFR, MAP, and 24-h urinary protein, and pathological features and lower C4 levels were related to Scr increased 1.5 times from the baseline. Conversely, Yang *et al*[11] found that decreased serum C3 in IgAN did not play a decisive role in reaching either ESRD or D-SCr. However, previous studies were all focused on the relationship between complements and eGFR decline or SCr elevation instead of ESRD and most of them were limited in the method that they focus on, and C3 or C4 alone may underestimate the function of complement in forecasting renal injury and patients' outcomes.

Our study showed that the C3/C4 ratio is related to the degree of proteinuria and SCr; the lower the ratio, the higher the proteinuria and SCr. In addition, the C3/C4 ratio is related to the G score and the T lesions. These findings may indicate that the C3/C4 ratio reflects the chronic renal injury in IgAN. We also evaluated the relationship between the C3/C4 ratio and the renal outcome of IgAN. The univariate Cox proportional hazard regression analyses indicated that the C3/C4 ratio is a risk factor for the poor prognosis of IgAN patients. However, when the data were adjusted for 24 h Upre, SCR, G, and T, its predicting efficiency disappeared, perhaps due to the differences at the baseline. Thus to avoid the selection bias, we conducted a PS matching. After performing a 1:1 PS matching, a total of 88 pairs of patients were enrolled. This approach showed that when

the differences of proteinuria and Scr disappeared at the baseline, the patients with the lowest C3/C4 ratio had a poorer outcome compared with the other group. This result strongly suggests that the C3/C4 ratio can be used as a biomarker of prognosis.

However, the PS matching has become a common and effective method for clinical studies. Here, we used this method to identify the risk factors for the prognosis of IgAN, which makes this approach different from previous retrospective studies. There are certain limitations to our study. First, this was a single-center study, and the sample was relatively small. Second, we could not detect the changes of complement levels and; therefore, could not evaluate their relevance for the patients' outcome. Third, we only found the relationship between the C3/C4 ratio and ESRD, but we did not assess its ability to forecast the eGFR decline. Studies with an expanded sample size and a longer follow-up period are needed to verify the conclusions of the present study.

In conclusion, IgAN patients with a decreased C3/C4 ratio displayed significantly more severe clinical symptoms and chronic renal injury than patients with higher ratios. A low C3/C4 ratio can be a risk factor for IgAN patients progressing to ESRD.

Funding

This work was supported by grants from the Science and Technology Project of Beijing China (No. D181100000118004, No. D181100000118002).

Conflicts of interest

None.

References

1. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. Clin J Am Soc Nephrol 2017;12:677–686. doi: 10.2215/CJN.07420716.
2. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, *et al*. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. Kidney Blood Press Res 2012;35:153–160. doi: 10.1159/000331453.
3. Caliskan Y, Ozluk Y, Celik D, Oztop N, Aksoy A, Ucar AS, *et al*. The clinical significance of uric acid and complement activation in the progression of IgA nephropathy. Kidney Blood Press Res 2016;41:148–157. doi: 10.1159/000443415.
4. Radford MG Jr, Donadio JV Jr, Bergstralh EJ, Grande JP. Predicting renal outcome in IgA nephropathy. J Am Soc Nephrol 1997;8:199–207.
5. Le W, Liang S, Chen H, Wang S, Zhang W, Wang X, *et al*. Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. Am J Nephrol 2014;40:43–50. doi: 10.1159/000364954.
6. Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis 2011;58:992–1004. doi: 10.1053/j.ajkd.2011.05.033.
7. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR. Human IgA activates the complement system via the mannan-binding lectin pathway. J Immunol 2001;167:2861–2868.
8. Zwirner J, Burg M, Schulze M, Brunkhorst R, Götze O, Koch KM, *et al*. Activated complement C3: a potentially novel predictor of progressive IgA nephropathy. Kidney Int 1997;51:1257–1264.
9. Kim SJ, Koo HM, Lim BJ, Oh HJ, Yoo DE, Shin DH, *et al*. Decreased circulating C3 levels and mesangial C3 deposition predict renal outcome in patients with IgA nephropathy. PLoS One 2012;7:e40495. doi: 10.1371/journal.pone.0040495.
10. Pan M, Zhang J, Li Z, Jin L, Zheng Y, Zhou Z, *et al*. Increased C4 and decreased C3 levels are associated with a poor prognosis in patients with immunoglobulin A nephropathy: a retrospective study. BMC Nephrol 2017;18:231. doi: 10.1186/s12882-017-0658-7.
11. Yang X, Wei RB, Wang Y, Su TY, Li QP, Yang T, *et al*. Decreased serum C3 levels in immunoglobulin A (IgA) nephropathy with chronic kidney disease: a propensity score matching study. Med Sci Monit 2017;23:673–681. doi: 10.12659/msm.903102.
12. Pan M, Zhou Q, Zheng S, You X, Li D, Zhang J, *et al*. Serum C3/C4 ratio is a novel predictor of renal prognosis in patients with IgA nephropathy: a retrospective study. Immunol Res 2018;66:381–391. doi: 10.1007/s12026-018-8995-6.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006.
14. Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. J Urol Nephrol (Paris) 1968;74:694–695.
15. Glassock RJ. The pathogenesis of IgA nephropathy. Curr Opin Nephrol Hypertens 2011;20:153–160. doi: 10.1097/MNH.0b013e3283436f5c.
16. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int 2004;66:920–923. doi: 10.1111/j.1523-1755.2004.00837.x.
17. Velo M, Lozano L, Egido J, Gutierrez-Millet V, Hernando L. Natural history of IgA nephropathy in patients followed-up for more than ten years in Spain. Semin Nephrol 1987;7:346–350.
18. Espinosa M, Ortega R, Sánchez M, Segarra A, Salcedo MT, González F, *et al*. Association of C4d deposition with clinical outcomes in IgA nephropathy. Clin J Am Soc Nephrol 2014;9:897–904. doi: 10.2215/CJN.09710913.
19. Komatsu H, Fujimoto S, Hara S, Sato Y, Yamada K, Eto T. Relationship between serum IgA/C3 ratio and progression of IgA nephropathy. Intern Med 2004;43:1023–1028. doi: 10.2169/internalmedicine.43.1023.
20. Ibels LS, Györy AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. Medicine (Baltimore) 1994;73:79–102. doi: 10.1097/00005792-199403000-00002.
21. Zhu B, Zhu CF, Lin Y, Perkovic V, Li XF, Yang R, *et al*. Clinical characteristics of IgA nephropathy associated with low complement 4 levels. Ren Fail 2015;37:424–432. doi: 10.3109/0886022X.2014.994408.

How to cite this article: Zhang Y, Duan SW, Chen P, Yin Z, Wang Y, Cai GY, Chen XM. Relationship between serum C3/C4 ratio and prognosis of immunoglobulin A nephropathy based on propensity score matching. Chin Med J 2020;133:631–637. doi: 10.1097/CM9.0000000000000674