Relationship between Serum IgA/C3 Ratio and Progression of IgA Nephropathy

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Abstract

Objective **The serum IgA/C3 ratio might be considered to serve as a diagnostic marker for patients with IgA nephropathy (IgAN), but its value as a marker of the severity of histological lesions or prognosis is unknown.**

Methods **We studied the serum IgA/C3 ratio, using standardized reference material, in 86 patients with IgAN and in 32 with non-IgAN. The patients with IgAN were divided according to the severity of histological lesions (mild IgAN, n=29 and severe IgAN, n=57) based on Japanese clinical guidelines.**

Results **The serum IgA level was significantly higher, while its C3 level was lower in patients with severe IgAN compared to those with non-IgAN. However, these levels were not different between patients with mild IgAN and non-IgAN. In contrast, the serum IgA/C3 ratio obviously differed among the three groups (2.47±0.96 vs. 3.63±1.44 vs. 4.72±1.86; $p<0.01$, ANOVA). Kaplan-Meier analysis of the patients with IgAN classified according to the mean serum IgA/C3 ratio revealed that the group with high serum IgA/C3 (4.5 and above) had a significantly poorer renal outcome ($p<0.05$, log-rank test), since the cumulative renal survival rate at 5 years was 84.4% vs. 100%. The ratio (%) of patients with severe IgAN in whom hematuria disappeared, was significantly higher in the low, than in the high serum IgA/C3 group (41.9% vs. 15.4%; $p<0.05$, t-test).**

Conclusion **The serum IgA/C3 ratio appears to reflect the histological severity of IgAN and could serve as a marker of the progression of IgAN.**

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Key words: IgA nephropathy, serum IgA/C3 ratio, serum IgA, complement, hematuria

Introduction

Berger and Hinglais originally described IgA nephropathy (IgAN) in 1968 as an immune-mediated glomerulonephritis (1). The condition is characterized by IgA deposition, predominantly in the glomerular mesangium, and it is frequently accompanied by the deposition of complement C3. Serum levels of IgA and of immune complexes bearing IgA in patients with IgAN are frequently elevated (2, 3), indicating that IgA plays a key role in the pathogenesis of renal injury (3). In contrast, serum C3 levels are usually normal or slightly increased (4), despite significant elevation of the plasma concentrations of C3 breakdown products and some evidence of C3 activation in the glomerular mesangium. What the IgA and C3 values represent, however, is obscure because measures for serum proteins have not been standardized.

In 1992, the International Federation of Clinical Chemistry (IFCC) published certified reference material (CRM) 470, as an international standard protein reference (5), and it was introduced into Japan in 1997 (6). Using this standard, Tomino et al (7) found that serum IgA and C3 might predict IgAN in patients before renal biopsy and recommended that a serum IgA level of over 315 mg/dl should be the diagnostic standard for IgAN. Moreover, the serum IgA/C3 ratio might predict prognostic grading in patients with IgAN (8). Here, we evaluated the value of the serum IgA/C3 ratio in assessing the prognosis of patients and the histological severity of IgAN.

For editorial comment, see p 1011.

Methods

Subjects

Serum IgA and C3 levels have been measured based on

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IFCC/CRM 470 at our hospital since November 1997. From then until April 2003, we diagnosed IgAN in 101 patients. After excluding those with nephrotic syndrome or inadequate serum IgA and C3 data, we selected 86 patients for further study who had no evidence of Henoch-Schönlein purpura nephritis, systemic lupus erythematosus, liver cirrhosis or other systemic diseases. The control group comprised 32 patients with non-IgAN without nephrotic syndrome (focal segmental glomerulosclerosis, n=11; minor glomerular abnormalities, n=11; membranous nephropathy, n=5; benign nephrosclerosis, n=3; membranoproliferative glomerulonephritis, n=2).

Measurement of serum IgA and C3

We collected blood samples and then immediately measured serum IgA and C3 levels using a turbidimetric immunoassay with reagents adjusted according to the IFCC/CRM 470. The serum IgA/C3 ratio was calculated from individual serum IgA and C3 values. The mean reported serum IgA/C3 ratio (for 418 healthy adults) is 1.89±1.13 (7).

Histological classification

We assessed the histological lesions of 86 patients with IgAN based on the guidelines presented by the Special Study Group (IgA nephropathy) on Progressive Glomerular Disease in Japan (9). These guidelines separate patients with IgAN into four prognostic groups:

1. Grade I (Good): Slight mesangial cell proliferation and increased matrix. Absence of glomerulosclerosis, crescent formation, and adhesion to Bowman's capsule. No prominent changes in the interstitium, renal tubuli, or blood vessels.

2. Grade II (Relatively good): Slight mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in less than 10% of all biopsied glomeruli. Interstitial and vascular findings the same as for grade I.

3. Grade III (Relatively poor): Moderate, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in 10–30% of all biopsied glomeruli. Cellular infiltration slight in the interstitium, except around some sclerosed glomeruli. Slight tubular atrophy and mild vascular sclerosis.

4. Grade IV (Poor): Severe, diffuse mesangial cell proliferation and increased matrix. Glomerulosclerosis, crescent formation, or adhesion to Bowman's capsule in more than 30% of all the biopsied glomeruli. When sclerosis sites are totaled and converted to global sclerosis, the sclerosis rate includes over 50% of glomeruli. Some glomeruli also show compensatory hypertrophy. Interstitial cellular infiltration and tubular atrophy, as well as fibrosis, are present. Some intrarenal arteriolar walls might be hyperplastic or degenerative.

We classified patients with grades I and II into a group with mild histological lesions (mild IgAN, n=29) and those with grades III and IV into a group with severe histological lesions (severe IgAN, n=57).

Immunoglobulin A was deposited in the glomerular mesangium of all patients whose IgAN was diagnosed using fluorescein isothiocyanate. We also semi-quantified the expansion of C3 co-deposition in the mesangial area and expressed it as negative, segmental or diffuse.

Definition of clinical findings

Hypertension was defined as systolic blood pressure ≧140 mmHg, and/or diastolic blood pressure ≧90 mmHg, or the use of anti-hypertensive medication. Nephrotic syndrome was defined as proteinuria (over 3.5 g/day) and hypoalbuminemia (below 3.0 g/dl) with or without hyperlipidemia or edema. Microscopic hematuria was defined as a positive dip-stick reaction (more than 1+) and urinary sediment (over 5–10 per high power field). Disappearance of hematuria and/or proteinuria was defined as at least two consecutive negative dip-stick reactions (– or ±).

Statistical analysis

All continuous variable data are presented as means± standard deviation (SD). Variable data with a normal distribution were compared among the three groups by a one-factor ANOVA with Scheffe's F test for post-hoc comparisons. Variable data were compared between two groups by Student's t-test when data were normally distributed or by Welch's t-test if the distribution was not normal. The chi-square test proved differences in data expressed as percentages between two or three groups. The relationship between continuous variables was investigated using Pearson's correlation coefficient. Renal survival rates in patients with IgAN were assessed by the Kaplan-Meier method. Differences in the survival curves of the high serum IgA/C3 and low ratio groups were analyzed by the log-rank test. A P value below 0.05 was considered statistically significant in all tests.

Results

Baseline patient characteristics

The patients with mild IgAN were younger than those with non-IgAN or with severe IgAN. More patients were hypertensive and proteinuria was more prevalent in the group with severe IgAN than in the mild IgAN group. Serum creatinine levels and macrohematuria episodes did not differ between the groups. The prevalence of hypertension or proteinuria and the serum creatinine levels also did not differ between non-IgAN and severe IgAN groups (Table 1).

Among the patients with mild IgAN, 9 (33.3%), 11 (37.9%) and 18 (62.1%) were treated with steroids, renin-angiotensin system inhibitors and tonsillectomy, respectively. Among those with severe IgAN, 33 (57.9%), 35 (61.4%) and 24 (42.1%) were respectively treated in the same manner.

Among these parameters, only age was positively correlated with serum IgA levels among the 86 patients with IgAN ($r=0.37$, $p<0.05$).

Table 1. Patient Baseline Characteristics

	Non-IgAN (n=32)	Mild IgAN (n=29)	Severe IgAN (n=57)	P value*
Age (years)	36.7±17.6	27.6±13.1†	36.4±13.6	0.02
Sex (M/F)	21/11	18/11	23/34‡	0.04
Hypertension	14 (43.8%)	1 (3.4%)§	16 (28.1%)	<0.01
Episodes of macrohematuria	1 (3.1%)	4 (13.8%)	10 (17.5%)	0.14
Proteinuria (g/day)	1.14±0.95	0.33±0.28‖	1.06±0.84	<0.01
Serum creatinine (mg/dl)	0.82±0.36	0.68±0.17	0.96±0.78	0.10

Mild IgAN: a group with Grade I and II assessed by histological classification. Severe IgAN: a group with Grade III and IV assessed by histological classification. All data are means±SD or number of patients (%, ratio of group). *Three groups assessed by one-factor ANOVA or chi-square. †$p<0.05$ vs. IgAN with severe lesions by Scheffe's F test. ‡$p<0.05$ vs. non-IgAN and IgAN with the mild lesions. §$p<0.01$ vs. non-IgAN and IgAN with severe lesions. ‖$p<0.01$ vs. non-IgAN and IgAN with severe lesions by Scheffe's F test.

Comparison of serum IgA, C3 levels and IgA/C3 ratios

The mean serum IgA level of the patients with severe IgAN was significantly higher than in the patients with non-IgAN or mild IgAN, but it did not differ between patients in the latter two groups (Fig. 1A). The mean serum C3 level for the patients with severe IgAN was significantly lower than that of the group with non-IgAN, but did not significantly differ from the value for mild IgAN (Fig. 1B). Serum IgA and C3 levels did not differ between non-IgAN and mild IgAN groups. In contrast, the serum IgA/C3 ratio obviously differed among the three groups, increasing in parallel with the histological severity of IgAN (2.47±0.96 vs. 3.63±1.44 vs. 4.72±1.86, $p<0.05$; Fig. 1C).

We compared serum IgA levels and serum IgA/C3 ratios between age-matched subgroups of patients with IgAN (mild lesions, n=22, 30.8±13.3 years; severe lesions, n=44, 31.4±10.8 years). The serum IgA/C3 ratios significantly differed between the two groups (3.73±2.09 vs. 4.79±1.87, $p<0.05$) whereas the serum IgA levels did not (315.9±135.9 vs. 370.9±117.0 mg/dl, $p=0.09$).

Correlation between mesangial C3 deposition and serum C3 levels

The immunofluorescence study showed C3 deposition in the glomerular mesangium in 68 of the 86 patients with IgAN (Table 2). The mean serum C3 value tended to decrease inversely, whereas the serum IgA/C3 ratio increased with C3 deposition. Moreover, the ratio of patients with IgG co-deposition was significantly higher in the group with diffuse C3 deposition than in those with negative or segmental C3 deposition (Table 2).

Relationship between renal survival and IgA/C3 ratio

The mean serum IgA/C3 ratio for all patients with IgAN was 4.36±1.79. We therefore compared the renal survival of patients based on serum IgA/C3 ratios of ≧ 4.5 (n=32) or <4.5 (n=54). Four patients with mean IgA/C3 ratios that were considerably above average (5.80±1.12) reached end-stage renal failure after the mean observation period of 30.6± 18.5 (6–69) months. Kaplan-Meier analysis revealed that the group with a high IgA/C3 ratio had a significantly poor renal outcome with a cumulative renal survival rate at 5 years being 84.4% vs. 100% (Fig. 2).

Comparison of severe IgAN in patients with high or low serum IgA/C3 ratios

Fifty-seven patients with severe IgAN were classified according to high (≧4.5, n=31) or low (<4.5, n=26) serum IgA/C3 ratios. Serum creatinine and proteinuria levels at the time of renal biopsy did not differ, but the ratio of the disappearance of hematuria was significantly higher in the group with a low, rather than a high IgA/C3 ratio (Table 3).

At 26.5±18.6 months of observation, the serum IgA/C3 ratio was re-examined in 27 of 57 patients with severe IgAN. It tended to be lower among those in whom hematuria had disappeared as compared with those in whom it persisted (2.59±0.89 vs. 3.11±1.11), but the difference was not significant.

Discussion

Because IgAN is considered an immune-mediated glomerulonephritis, the severity of histological lesions might be related to immunological activity, as in lupus nephritis. However, whether the serum IgA or C3 level is related to histological damage in IgAN remains unknown. We examined whether the serum IgA/C3 ratio is elevated in association with immunological activity. We found that the serum IgA/C3 ratio was significantly higher in patients with severe IgAN than in those with mild IgAN or non-IgAN. Furthermore, the renal survival was significantly poorer in IgAN patients with a high (above 4.5) serum IgA/C3 ratio.

Abnormal IgA synthesis is both qualitatively and quantitatively related to the pathogenesis of IgAN. Lymphocytes from the secretory tissues of patients with IgAN after viral infection produce large amounts of polymeric IgA (10) and the tonsillar tissues of patients with IgAN contain a significantly increased number of IgA-positive cells (11). The

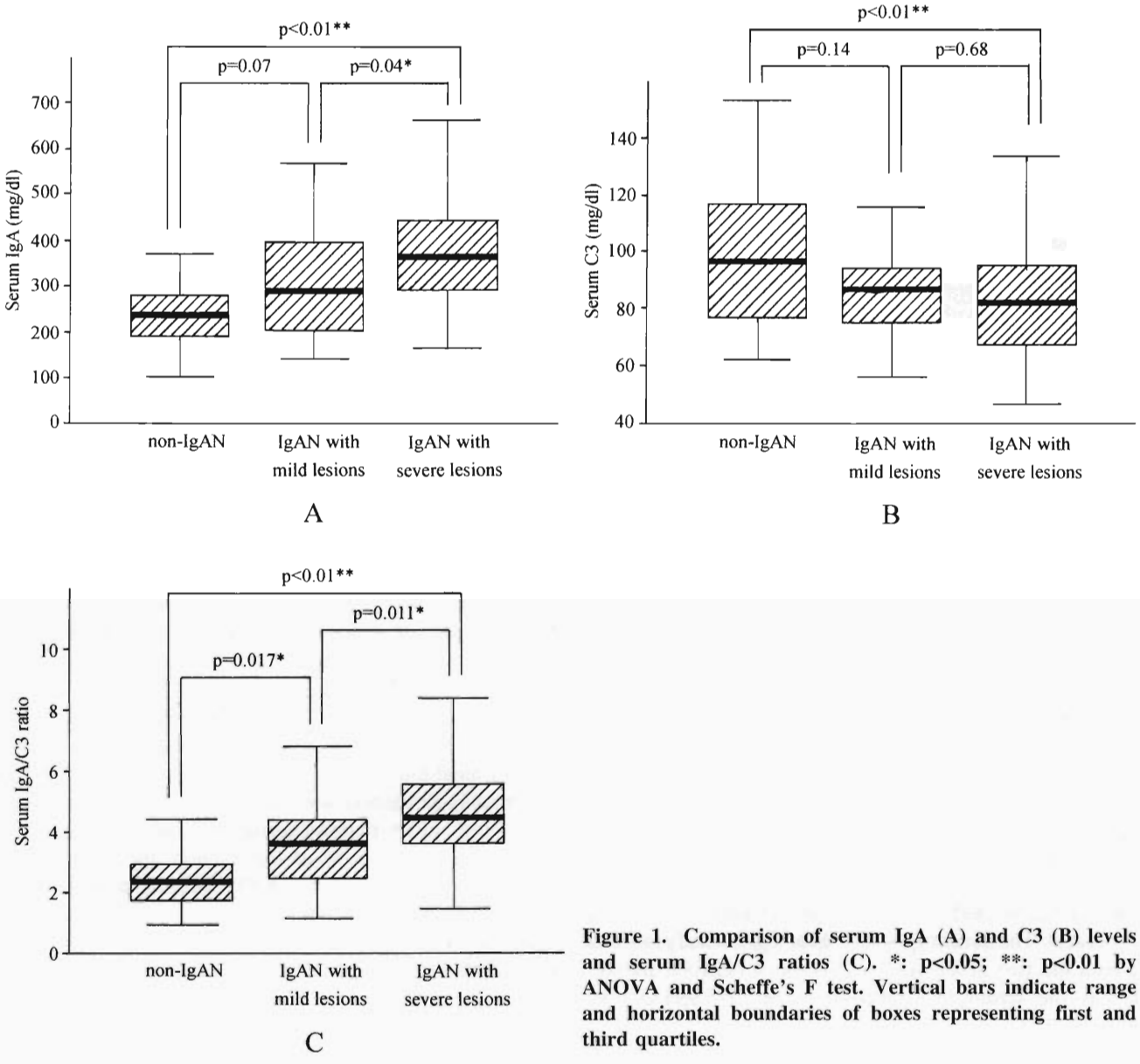

Figure 1. Comparison of serum IgA (A) and C3 (B) levels and serum IgA/C3 ratios (C). *: p<0.05; **: p<0.01 by ANOVA and Scheffe's F test. Vertical bars indicate range and horizontal boundaries of boxes representing first and third quartiles.

Table 2. Correlation between C3 Deposition in Glomerular Mesangium and Serum IgA and C3 Levels

	C3 deposition			P value*
	Negative (n=18)	Segmental (n=38)	Diffuse (n=30)	
Serum C3 (mg/dl)	92.4±25.0	86.3±21.2	81.2±18.3	0.21
Serum IgA (mg/dl)	337.5±119.6	348.8±115.5	357.2±120.7	0.86
Serum IgA/C3 ratio	3.90±1.24	4.32±1.83	4.62±1.92	0.37
Co-deposition of IgG	1 (5.6%)	5 (13.2%)	10 (33.3%)†	<0.05
Severe histological lesions	7 (38.9%)	26 (68.4%)‡	24 (80.0%)‡	<0.05

All data are means±SD or number of patients (%, ratio of group). *The three groups assessed by a one-factor ANOVA or chi-square test. †p<0.05 vs. negative and segmental C3 deposition. ‡p<0.05 vs. negative C3 deposition.

isoelectric focusing profile of IgA obtained from tonsillar extract well overlaps that of serum (12). Moreover, IgA1 molecules produced by tonsillar lymphocytes of patients with IgAN are under-glycosylated (13). In contrast, the increased amount of IgA plasma cells in the bone marrow is correlated with the serum IgA level (14–16). Additionally, bone mar-

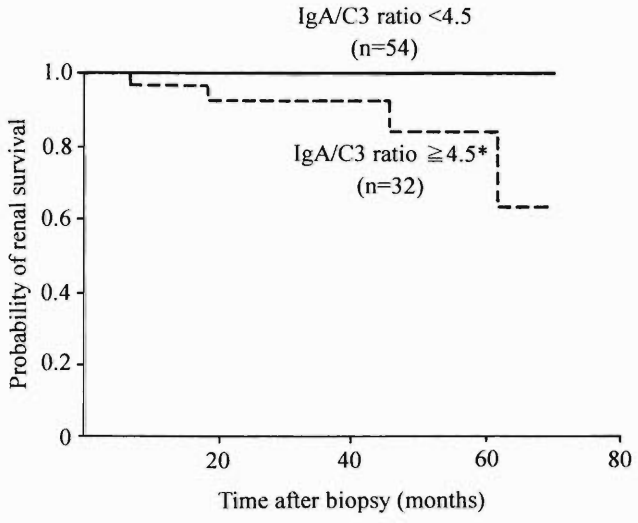

Figure 2. Kaplan-Meier analysis of cumulative renal survival of patients with IgA nephropathy based on serum IgA/C3 ratio (mean level: 4.36) at renal biopsy. Survival curves significantly differ (*: p<0.05, log-rank test).

row transplantation from normal mice into a murine model of IgAN (high serum IgA ddY mouse; HIGA mouse), replaces the recipient's immune cells and regenerates glomerular cells (17, 18). Thus, the amount and class distribution of plasma cells from the mucosa and bone marrow (the mucosa-marrow axis) support the contention that IgA plays an important role in the pathogenesis of IgAN (19). The present study and other studies have shown that half of all reported patients with IgAN have elevated serum IgA levels (19, 20). However, the relationship between the serum IgA level and severity of IgAN remains obscure. The present study could not confirm that the serum IgA level alone can clearly differentiate severe from mild lesions among patients with IgAN. On the other hand, we confirmed a slightly positive correlation between serum IgA level and age. The difference in the serum IgA levels between patients with mild and severe IgAN was diminished in an age-matched comparison, whereas, the serum IgA/C3 ratio remained significantly higher in patients with severe, compared to mild IgAN. This finding implies that the progression of IgAN causes the serum C3 level to decrease through activation of the complement system.

Activation of the complement system, especially of the alternative pathway, corresponds to abnormal synthesis of IgAN. This is reflected mainly by increases in C3 breakdown products such as C3a (21), iC3b-C3d (4), and activated C3 (22, 23) in serum or plasma. We found that diffuse C3 deposition in the glomerular mesangium is related to a low serum C3 level, IgG co-deposition, and severe histological lesions. Waldo (3) suggested that IgG locates at sites of complement fixation, and that local complement activation mediated by deposited IgG is essential to mesangial cell proliferation and subsequent renal injury. In fact, mesangial IgG deposition is a reported risk factor for hypertension and renal failure in IgAN (24). Considering these factors, C3 consumption appears to be essential for the progression of IgAN. The serum C3 level in the present study tended to be lower in patients with IgAN than in non-IgAN patients, but patients with severe or mild histological lesions could not be differentiated.

Thus, whether the serum IgA and C3 levels reflect the severity of IgAN is questionable. This might be due partly to differences in assays and reagents and to comparisons with standards other than an international reference material such as CRM 470. Tomino et al (7) reported that serum IgA and C3 levels measured based on CRM470 were significantly higher and lower, respectively, in 195 patients with IgAN

Table 3. Comparison of High and Low Serum IgA/C3 Ratios in Patients with Severe IgA Nephropathy

	Serum IgA/C3 ratio <4.5 (n=31)	Serum IgA/C3 ratio ≧4.5 (n=26)	P value*
BASELINE			
Age (years)	32.8±15.1	34.5±12.2	0.57
Serum IgA/C3 ratio	3.43±0.76	6.03±1.45	<0.01
Serum creatinine (mg/dl)	0.87±0.37	1.09±1.08	0.29
Proteinuria (g/day)	1.06±0.70	1.07±1.00	0.96
FINAL FOLLOW-UP			
Observation period (months)	27.0±17.5	35.5±19.0	0.09
Disappearance of hematuria	13 (41.9%)‡	4 (15.4%)	<0.05
Disappearance of proteinuria	12 (38.7%)	8 (30.8%)	0.53
TREATMENT			
Tonsillectomy	16 (51.6%)	8 (30.8%)	0.11
Corticosteroid	22 (71.0%)†	11 (42.3%)	<0.05
ACE-I and/or ARB	20 (64.5%)	15 (57.7%)	0.60

All data are means±SD or number of patients (%, ratio of group). *Two groups assessed by t-test or chi-square test. †p<0.01 by t-test, ‡p<0.05 by chi-square test.

than with non-IgAN and healthy controls. They also indicated that applying the ratio of serum IgA to C3 to diagnosing IgAN improves both sensitivity and specificity. Ishiguro et al (8) reported that the serum IgA/C3 ratio appears to increase according to the prognostic grading of IgAN based on their recalculated serum IgA and C3 levels, but differences among the graded groups were not statistically significant.

Our results show that the serum IgA/C3 ratio not only distinguishes between IgAN and other primary glomerular diseases, but it also reflects the pathological severity of IgAN. In addition, this ratio differentiates more clearly, than does serum IgA or C3 alone, IgAN with severe or mild histological lesions.

We found that urinary abnormalities, especially hematuria, more frequently disappeared in patients with a low serum IgA/C3 ratio. Our study apparently included the IgAN patients with mild histological lesions. Because mild IgAN sometimes spontaneously undergoes clinical remission (25), we assessed the effect of treatment on urinary abnormalities in IgAN patients with severe histological lesions and proteinuria above 1.0 g/day. However, this retrospective study could not confirm that hematuria disappears less frequently in patients with a high serum IgA/C3 ratio because their frequency of steroid drug consumption was significantly lower (Table 3). Patients with nephrotic syndrome were excluded from this study because some serum IgA is lost to the urine. We could not therefore evaluate the value of the serum IgA/C3 ratio for IgAN patients with nephrotic range proteinuria.

In summary, the serum IgA/C3 ratio appears to predict disease severity among patients with non-nephrotic IgAN. To our knowledge, we are the first to show that a high serum IgA/C3 ratio ($\geq$ 4.5) might be related to a poor prognosis for patients with IgAN based on an estimation of the actual renal survival rate. However, long-term follow-up is required to assess the validity of this marker and further studies should clarify whether or not the serum IgA/C3 ratio also reflects the effectiveness of treatment for IgAN.

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