

Hypocomplementemia (C3) as an independent predictor for children with acute post-streptococcal glomerulonephritis: a long-term observation

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Abstract. – OBJECTIVE: The aim of this study was to examine the altering patterns in clinical characteristics and severity of acute post-streptococcal glomerulonephritis (APSGN) in children.

PATIENTS AND METHODS: We analyzed the medical records of 119 children who were diagnosed with APSGN from 1987 to 2018, retrospectively. The patients were divided into two groups: Group I (n=72, before 1998) and Group II (n=47, after 1998). Clinical, radiologic, and laboratory findings were compared between the two groups.

RESULTS: The clinical manifestations, including vomiting (20.8% vs. 4.3%, $p=0.014$), oliguria (40.3% vs. 19.1%, $p=0.016$), and generalized edema (86.1% vs. 63.8%, $p=0.005$), were statistically less frequent since 1998. Pulmonary edema on chest X-ray (22.7% vs. 4.4%, $p=0.014$) was less frequent in Group II than in Group I. The level of BUN (23.3 ± 19.3 vs. 18.8 ± 11.2 , $p=0.009$) was lower in Group II than in Group I, while that of creatinine was not significantly different between the two groups. C3 level was an independent factor for predicting the development of edema (odds ratio [OR]: 1.034, 95% CI: 1.010-1.060, $p=0.006$) and

acute nephritic symptoms (≥ 2) (OR: 0.974, 95% CI: 0.952-0.996, $p=0.020$). It was also negatively correlated with an increasing number of acute nephritic symptoms, including oliguria and edema, in patients with APSGN ($R=-0.182$, $p=0.048$).

CONCLUSIONS: This study demonstrated that APSGN had favorable clinical manifestations and severity over the past 30 years. The monitoring of C3 levels can be used to assess the disease severity and risk of complications, including edema and oliguria, which are decreasing in South Korean children.

Key Words:

Streptococcal infection, Acute glomerulonephritis, Complement C3, Edema.

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is an inflammatory response to infection in the renal glomeruli, characterized by the sudden onset of edema, hematuria, proteinu-

ria, and hypertension. APSGN is a syndrome that is accompanied by urinary findings of nephritis¹. It is a common complication that accounts for approximately 90% of renal disorders in children². The disease occurs particularly in those between 2 and 12 years of age and young adults, and more often in males than in females². APSGN is caused by an infection with group A beta hemolytic streptococci and upper airway infections, such as pharyngitis or tonsillitis. Moreover, infection of the skin precedes APSGN, usually 3 weeks after clinical manifestation². The infection causes antibodies and complement proteins to activate and aggravate blood vessels in the kidneys, which is an immune-complex-mediated mechanism².

APSGN can also lead to rapidly progressive glomerulonephritis within a few weeks or months to end-stage renal failure¹. Nephrotic-range proteinuria, renal insufficiency at the onset, and crescents in more than one-third of the glomeruli are related to a poor prognosis¹. Necrotizing crescentic glomerulonephritis is often observed in histopathological findings¹. The clinical concept of rapidly progressive glomerulonephritis implies various renal diseases that cause renal function to worsen over a subacute course.

In recent decades, the number of patients with post-streptococcal glomerulonephritis has decreased considerably in industrialized countries³. However, in some developing communities, the incidence of PSGN remains high. APSGN is one of the leading causes of hospital admissions in developing countries and is also an important factor for acute kidney injury in children. Although mortality due to this disease is low, it can cause serious complications, including congestive heart failure, renal disorder, pulmonary edema, encephalopathy, and hypertensive emergency⁴.

Previous literature has suggested that the number of patients with APSGN has decreased in South Korean children with no change in the severity of the syndrome^{5,6}. However, these studies had the limitation of being performed over a short duration (<10 years). Therefore, the present study aimed to investigate whether there were different clinical manifestations and outcomes over a longer-term, of over 30 years, in South Korean children.

Patients and Methods

Study Design and Population

We retrospectively analyzed the medical records of 119 children (aged 2-16 years) (55 girls

and 64 boys, aged 22-192 months; mean age of 99.3±33.4 months) with APSGN who visited Severance Hospital in South Korea over a period of 30 years between January 1987 and December 2018. We included patients with a typical clinical course of the disease, including antecedent pharyngitis or skin pyoderma followed by gross hematuria, proteinuria, edema, or hypertension.

APSGN was diagnosed in the presence of the following: 1) evidence of streptococcal infection, 2) lower serum complement three levels, and 3) features of acute nephritic syndrome. Anti-streptolysin-O (ASO) titer >200 IU/mL was considered as evidence of recent streptococcal infection. A decreased level of serum complements three that returned to normal within 6-8 weeks after the onset of APSGN and an increased level of ASO >200 IU/mL were strongly suggestive of APSGN. Patients with other forms of glomerulonephritis, including IgA nephropathy, hereditary nephritis, membranoproliferative glomerulonephritis, and lupus nephritis, were excluded from this study. Patients treated from 1987 to 1997 were classified as Group I and those after 1998 as Group II.

Clinical Data Extraction

Demographic data and symptoms (gross or microscopic hematuria, edema, headache, vomiting, convulsion, fever, dyspnea, abdominal pain, and oliguria) and signs (hypertension and costovertebral angle tenderness) at initial clinical presentation were reviewed. Laboratory tests included complete blood cell counts, erythrocyte sedimentation rate, C-reactive protein, blood urea nitrogen (BUN), creatinine (Cr), ASO titer, immunoglobulin (Ig) G, IgA, IgM, complement 3 (C3) and 4 (C4), and 24-hr protein excretion. The chest X-ray was reviewed by a radiologist, and increased pulmonary vascularity, cardiomegaly, pulmonary edema, and pleural effusion were recorded.

Acute nephritic features were defined as oliguria, edema or hypertension, and a rapid reduction in the glomerular filtration rate due to glomerular disorder. Severe acute nephritic features were defined as having two or more signs of acute nephritic syndrome among oliguria, edema, and hypertension. Oliguria was defined as a urine output of less than 1 mL/kg/h in infants and less than 0.5 mL/kg/h in children, or 500 mL/1.73 m² per day. Edema was classified as generalized edema, eyelid edema, or pitting edema. The diagnosis of hypertension was made when blood pressure values were greater than the 95th percentile for age, sex, and height of the patient, or when they were

$\geq 130/80$ mmHg⁷. Microscopic hematuria was regarded as five or more red blood cells upon urine microscopy. Cardiomegaly was considered as a cardiothoracic ratio >0.5 on chest X-ray. The descriptive data are expressed as number and percent.

Statistical Analysis

Statistical analyses were performed using the IBM Statistics Package for the Social Science (SPSS) version 18.0 for Windows (IBM Corporation, Armonk, NY, USA) and MedCalc version 15.8 (MedCalc Software, Ostend, Belgium). Independent *t*-test was used for continuous variables, and values are expressed as mean \pm standard deviation. Chi-square test and Fisher's exact test were used to analyze categorical variables. Correlation analysis was also performed to determine the relationship between two variables by Spearman correlation. Multiple logistic regression analysis was used to find the independent predictive factors for severe acute nephritic syndrome in children with APSGN.

Results

Demographics and clinical data are shown in Table I. We categorized the patients according to years; 1987-1997 was classified as Group I, and 1998-2018 as Group II. The number of patients

was 72 in Group I and 47 in Group II. There were no significant differences according to the age at disease onset and sex between the two groups. In addition, the sites of prior streptococcal infection were not different between Group I and Group II. Among the symptoms and signs of APSGN, vomiting (20.8% vs. 4.3%, $p=0.014$), oliguria (40.8% vs. 19.1%, $p=0.016$), and edema (86.1% vs. 63.8%, $p=0.005$) were more frequent in the patients before 1998 than in those after 1998. Other symptoms and signs, such as fever, dyspnea, abdominal pain, or gross hematuria, did not differ between the two groups.

On chest X-rays, pulmonary edema was less frequent in Group II than in Group I (22.7% vs. 4.4%, $p=0.014$). Other findings (increased pulmonary vascularity, pleural effusion, and cardiomegaly) showed no significant difference between the two groups (Table II).

Laboratory findings of the patients were presented in Table III. Serum BUN levels in Group I were significantly higher than those in group II (23.3 \pm 19.3 vs. 18.8 \pm 11.2, $p=0.009$), and serum C3 levels in Group I were lower (21.7 \pm 17.4 vs. 30.3 \pm 22.2, $p=0.044$), while the levels of other parameters, including Cr, ASO, and C4, did not differ between the two groups.

We divided the patients again into four groups according to the number of acute nephritic symptoms; patients without acute nephritic symptoms and patients with one, two, and all nephri-

Table I. Demographics and clinical manifestations of patients with APSGN.

Variables	Group I (%) (n=72)	Group II (%) (n=47)	<i>p</i> -value
Age (months)	100 \pm 33	100 \pm 34	0.715
Sex (Male/Female)	39/33	25/22	0.917
Preceding infections			
Acute pharyngitis	45 (62.5)	30 (63.8)	0.883
Skin infection	0 (0.0)	1 (2.1)	0.395
Symptoms and signs			
Fever	10 (13.9)	6 (12.8)	0.861
Dyspnea	10 (13.9)	3 (6.4)	0.242
Headache	5 (6.9)	3 (6.4)	1.000
Convulsion	0 (0.0)	1 (2.1)	0.395
Vomiting	15 (20.8)	2 (4.3)	0.014
Abdominal pain	14 (19.4)	6 (12.8)	0.341
Abdominal distension	3 (4.2)	1 (2.1)	0.652
Gross hematuria	47 (65.3)	28 (59.6)	0.529
Oliguria	29 (40.3)	9 (19.1)	0.016
Edema	62 (86.1)	30 (63.8)	0.005
Hypertension	58 (80.6)	33 (70.2)	0.194
CVA tenderness	11 (15.3)	3 (6.4)	0.160
Crackle	3 (4.2)	5 (10.6)	0.261

APSGN, acute post-streptococcal glomerulonephritis; CVA tenderness, costovertebral angle tenderness

Table II. Chest X-ray findings of patients with APSGN.

Findings	Group I (%) (n = 66)	Group II (%) (n = 45)	p-value
Normal	39 (59.1)	35 (77.8)	0.040
Increased pulmonary vascularity	8 (12.1)	5 (11.1)	0.871
Pulmonary edema	15 (22.7)	2 (4.4)	0.014
Pleural effusion	9 (13.6)	7 (15.6)	0.777
Cardiomegaly	3 (4.5)	3 (6.7)	0.685

Laboratory findings of the patients are presented in Table III. Serum BUN levels in Group I were significantly higher than those in Group II (23.3±19.3 vs. 18.8±11.2, $p=0.009$), and serum C3 levels in Group I were lower (21.7±17.4 vs. 30.3±22.2, $p=0.044$), while the levels of other parameters, including Cr, ASO, and C4, did not differ between the two groups.

Table III. Laboratory findings of patients with APSGN.

	Group I (%)	Group II (%)	p-value
BUN (mg/dL)	23.3 ± 19.3	18.8 ± 11.2	0.009
Cr (mg/dL)	0.9 ± 0.7	0.7 ± 0.3	0.067
ASO (mg/dL)	628 ± 763	872 ± 859	0.189
IgG (mg/dL)	1465.7 ± 369.2	1319.5 ± 432.3	0.951
IgA(mg/dL)	210.0 ± 85.0	167.4 ± 68.9	0.177
IgM (mg/dL)	177.0 ± 63.1	136.0 ± 66.8	0.953
C3 (mg/dL)	21.7 ± 17.4	30.3 ± 22.2	0.044
C4 (mg/dL)	26.1 ± 14.9	22.0 ± 13.3	0.143
Proteinuria (mg/day)	1030.6 ± 1784.1	975.8 ± 1760.6	0.879
Cardiomegaly	3 (4.5)	3 (6.7)	0.685

BUN, blood urea nitrogen; Cr, serum creatinine; ASO, anti-streptolysin O; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement component 3; C4, complement component 4.

tic symptoms. Table IV shows the demographic, clinical, and radiologic findings of these newly categorized groups. There were significant differences between the four groups in terms of oliguria ($p<0.0001$), edema ($p<0.0001$), hypertension ($p<0.0001$), abdominal distension ($p=0.004$), and gross hematuria ($p<0.0001$). All other demographics, including age, sex, preceding infection sites, and clinical characteristics, did not differ between the groups. In the comparison between less than one nephritic symptom and more than two nephritis symptoms, there were significant differences in oliguria ($p=0.002$), edema ($p<0.0001$), hypertension ($p<0.0001$), and gross hematuria ($p<0.0001$). However, abdominal distension showed no difference ($p=0.319$). We performed further analysis to see whether there were any differences between less than two nephritic symptoms and more than three nephritis symptoms and found that oliguria ($p<0.0001$), edema ($p=0.001$), hypertension ($p=0.001$), and abdominal distension ($p=0.002$) had significant differences, while gross hematuria did not ($p=0.245$). However, among laboratory findings of these

newly categorized groups, only serum C3 levels were significantly lower in groups with three nephritic symptoms than in those with less than two nephritic symptoms (Table V).

Multiple logistic regression analyses showed that serum C3 level was an independent predictive factor for developing edema (odds ratio: 1.034, 95% CI: 1.010-1.060, $p=0.006$) in patients with APSGN (Table VI). Under different cut-off values of C3, the sensitivity, specificity, positive predictive values, negative predictive values, as well as positive and negative likelihood ratio of C3 were examined. A C3 cut-off value of 20.3 mg/dL yielded a moderate sensitivity and specificity of 60.9% and 70.4%, respectively. When a cut-off value of 29 mg/dL was shown, the sensitivity increased to 75.0%, while the specificity decreased to 48.15% (Table VII).

Discussion

APSGN is one of the most important types of glomerulonephritis in children. Although epidemics of APSGN have been occurring worldwide,

its overall incidence has decreased in advanced countries². Improved hygienic conditions and increased use of antibiotics are believed to prevent streptococcal infections and decrease related morbidity and mortality^{3,4}. The prevalence of APSGN is also decreasing worldwide, and epidemic outbreaks of APSGN have declined^{2,3,8}. Repeated streptococcal infections and vaccines among

young children have resulted in some degree of herd immunity and evolved into less virulent strains of GAS³. The virulence of GAS may be milder since the clinical manifestations of APSGN have generally been less severe and the mortality rate lower in recent years³. Factors such as crowding, poor hygiene, and poverty have contributed to APSGN outbreaks⁹. Indeed, better living

Table IV. Demographic, clinical and radiologic findings of patients with APSGN according to the number of acute nephritic symptoms.

Variables	No ANS (%) (n=7)	One ANS (%) (n=28)	Two ANS (%) (n=59)	Three ANS (%) (n=25)	p-value (4 groups)	p-value (≤1 vs. ≥2 ANS)	p-value (≤2 vs ≥3 ANS)
Age (months)	84 ± 26	99 ± 38	103 ± 35	99 ± 27	0.545	0.361	0.885
Sex (Male/Female)	3/4	17/11	34/25	10/15	0.378	0.690	0.175
Preceding infections							
Acute pharyngitis	4 (57.1)	17 (60.7)	39 (66.1)	15 (60)	0.891	0.681	0.817
Skin infection	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.059	0.294	1.000
Symptoms and signs							
Fever	3 (42.9)	3 (10.7)	5 (8.5)	5 (20.0)	0.066	0.556	0.324
Dyspnea	0 (0.0)	3 (10.7)	8 (13.6)	2 (8.0)	0.907	0.753	0.734
Headache	0 (0.0)	2 (7.1)	5 (8.5)	1 (4.0)	0.934	1.000	1.000
Convulsion	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1.000	1.000	1.000
Vomiting	0 (0.0)	4 (14.3)	10 (16.9)	3 (12.0)	0.848	0.775	1.000
Abdominal pain	0 (0.0)	4 (14.3)	11 (18.6)	5 (20.0)	0.746	0.423	0.764
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	4 (16.0)	0.004	0.319	0.002
Gross hematuria	7 (100)	25 (89.3)	30 (50.8)	13 (52.0)	<0.0001	<0.0001	0.245
Oliguria	0 (0.0)	4 (14.3)	9 (15.3)	25 (100)	<0.0001	0.002	<0.0001
Edema	0 (0.0)	10 (35.7)	57 (96.6)	25 (100)	<0.0001	<0.0001	0.001
Hypertension	0 (0.0)	14 (50.0)	52 (88.1)	25 (100)	<0.0001	<0.0001	0.001
CVA tenderness	0 (0.0)	4 (14.3)	7 (11.9)	3 (12.0)	0.941	1.000	1.000
Crackle	0 (0.0)	1 (3.6)	3 (5.1)	4 (16.0)	0.310	0.434	0.059
CVA tenderness	0 (0.0)	4 (14.3)	7 (11.9)	3 (12.0)	0.941	1.000	1.000
Crackle	0 (0.0)	1 (3.6)	3 (5.1)	4 (16.0)	0.310	0.434	0.059
Abnormal X-ray	0 (0.0)	5 (19.2)	22 (40.0)	10 (43.5)	0.041	0.015	0.321

ANS, acute nephritic symptoms; CVA tenderness, costovertebral angle tenderness

Table V. Laboratory findings of patients with APSGN according to the number of acute nephritic symptoms.

Variables	No ANS (%) (n=7)	One ANS (%) (n=28)	Two ANS (%) (n=59)	Three ANS (%) (n=25)	p-value (4 groups)	p-value (≤1 vs. ≥2 ANS)	p-value (≤2 vs ≥3 ANS)
BUN (mg/dL)	13.8±4.3	20.8±13.1	20.5±13.4	26.7±26.1	0.244	0.377	0.233
Cr (mg/dL)	0.5±0.1	0.8±0.3	0.8±0.7	0.9±0.6	0.567	0.386	0.417
ASO (mg/dL)	536±79	859±938	746±901	575±444	0.565	0.544	0.299
IgG (mg/dL)	1274.4±233.3	1496.8±538.2	1407.5±380.6	1341.6±302.1	0.519	0.443	0.393
IgA (mg/dL)	145.8±34.0	210.2±102.2	190.6±79.3	193.4±68.7	0.380	0.756	0.974
IgM (mg/dL)	141.2±74.6	150.4±54.5	166.3±74.3	160.7±61.2	0.723	0.283	0.991
C3 (mg/dL)	41.2±27.2	27.1±20.0	24.5±20.4	19.6±13.0	0.073	0.084	0.044
C4 (mg/dL)	26.8±7.5	24.4±9.8	24.8±15.7	23.1±17.1	0.938	0.843	0.604
Proteinuria (mg/day)	446.1±452.7	1400.8±2401.6	1008.2±1815.1	759.6±846.8	0.529	0.472	0.444

ANS, acute nephritic symptoms; BUN, blood urea nitrogen; Cr, serum creatinine; ASO, anti-streptolysin O; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement component 3; C4, complement component 4.

Table VI. Multiple logistic regression analysis of risk for various acute nephritic symptoms in patients with APSGN.

	Oliguria		Edema		Hypertension		ANS ≥ 2		ANS ≥ 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
ASO	1.001 (1.000-1.001)	0.180	1.000 (0.999-1.001)	0.940	0.999 (0.997-1.000)	0.123	1.000 (0.999-1.001)	0.954	1.000 (0.999-1.001)	0.763
IgG	0.999 (0.998-1.000)	0.088	1.002 (1.000-1.003)	0.0340	1.001 (1.000-1.003)	0.117	0.999 (0.998-1.001)	0.330	0.999 (0.998-1.001)	0.478
IgA	1.003 (0.997-1.009)	0.310	0.996 (0.989-1.004)	0.340	1.000 (0.994-1.007)	0.885	0.998 (0.992-1.004)	0.516	1.000 (0.994-1.007)	0.960
IgM	0.996 (0.990-1.003)	0.282	0.996 (0.988-1.004)	0.351	1.000 (0.992-1.007)	0.906	1.006 (0.998-1.013)	0.156	1.001 (0.993-1.009)	0.875
C3	1.016 (0.991-1.041)	0.224	1.034 (1.010-1.060)	0.006	1.018 (0.993-1.043)	0.153	0.974 (0.952-0.996)	0.020	0.974 (0.943-1.006)	0.105
C4	0.990 (0.958-1.024)	0.564	0.996 (0.957-1.037)	0.836	1.010 (0.974-1.047)	0.592	1.003 (0.966-1.042)	0.857	1.004 (0.964-1.046)	0.849

OR, odds ratio; CI, confidence interval; ANS, acute nephritic symptoms; BUN, blood urea nitrogen; Cr, serum creatinine; ASO, anti-streptolysin O; IgG, immunoglobulin G; C3, complement component 3; C4, complement component 4.

Table VII. Diagnostic accuracy of C3 for predicting edema formation in patients with APSGN.

Variables	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
C3 ≤ 20.3 (mg/dL)	60.9 (50.1-70.9)	70.4 (49.8-86.2)	18.6 (8.0-34.3)	94.2 (86.6-98.2)	2.05 (1.1-3.8)	0.56 (0.4-0.8)
C3 ≤ 25 (mg/dL)	66.3 (55.7-75.8)	59.3 (38.8-77.6)	15.3 (6.8-28.1)	94.1 (85.5-98.4)	1.63 (1.0-2.6)	0.57 (0.4-0.9)
C3 ≤ 29 (mg/dL)	75.0 (64.9-83.4)	48.15 (28.7-68.1)	13.8 (6.5-24.7)	94.5 (84.8-98.9)	1.45 (1.0-2.1)	0.52 (0.3-0.9)

LR, likelihood ratio; NPV, negative predictive values; PPV, positive predictive values.

conditions, less crowding, and wider living space have led to fewer opportunities for person-to-person spread of streptococcal infections³.

Two South Korean studies^{5,6}, which were published before 2006, showed no significant difference in the clinical aspects of APSGN. However, both studies had a short follow-up period (<10 years). Kuem et al¹⁰ reported that the annual incidence of APSGN has decreased since 2000, and the prevalence of infection-related immune-mediated diseases could change over time. The annual incidence was investigated over a period of 30 years in the present study, and we found that the incidence of APSGN had significantly decreased since 1998 (not included), as observed in a previous study. Therefore, the groups were classified on the basis of using the year 1998 as the cut-off point. This study demonstrated that the severity of APSGN after 1998 was milder compared to before 1998 in South Korea.

The authors collected additional meaningful clinical findings, which were not reported in the previous literature, in order to analyze significant correlations and identify the independent risk factors. Koo et al⁵ reported that there were no clinical differences in APSGN, including the age at onset, gender, seasonal variation, preceding infection, early clinical manifestations, or complications of the acute phase, between the years 1994 and 2003 in South Korea. Choi et al⁶ identified that children with APSGN in the years 2001-2006 had higher levels of ASO titer compared to those in the years 1992-2000; however, no remarkable differences were observed in the clinical courses of APSGN.

The present study showed that clinical patterns of APSGN in children have changed over the years and that clinical manifestations were less severe in 1998-2018 as compared to 1987-1997. Children presenting with APSGN between 1998 and 2018 had a lower frequency of generalized edema, oliguria, and hypertension compared to children with APSGN between 1987 and 1997. ASO titer was not significantly different between before and after 1998, while serum C3 level was lower in children with APSGN before 1998 compared to after 1998. Vomiting was more commonly observed in Group I, which is considered to be a sign of volume overload due to GFR reduction and be accompanied by nephritic features such as oliguria and edema. Therefore, these findings can be emphasized to the clinician to carefully observe hypertension or hypertensive encephalopathy in APSGN.

Interestingly, BUN level, but not creatine level, was significantly different between Groups I and

II. The renal involvement of APSGN is developed at the acute onset, and patients with vomiting, edema, or oliguria usually visit the hospital at the early phase. Careful attention should be given to an elevated BUN level, even though the level of serum creatinine is within normal limits. Gross hematuria was more frequently observed in the group without acute nephritic symptoms than in the group with acute nephritic symptoms. Lee et al¹¹ reported that approximately 90% of patients with recurrent gross hematuria had no proteinuria at follow-up, and gross hematuria completely resolved in 97% of patients. According to the present study (Table IV), gross hematuria could be considered as a good prognosis sign in APSGN.

GAS has been serologically classified based on the Lancefield M protein serotyping system^{12,13}. Recently, M protein gene (*emm*) typing has been used for the classification of GAS¹⁴. The M protein is also known to prevent bacterial opsonization via the alternative complement pathway¹⁵. Type 12 is associated with the most frequent GAS M serotype which causes APSGN after streptococcal pharyngitis, whereas M 49 is the type related to pyoderma-associated APSGN¹². M type 1 is the most common, followed by types 4, 12, and 6; and the proportion of isolates of type 12 has decreased over time¹⁴. In South Korea, some studies have shown varying trends of M protein genes over time. However, whether these variations are relevant to the changing severity of acute nephritic features in APSGN remains unexplored^{16,17}. Although we did not examine the virulence of *emm* genotyping in patients with APSGN, the dynamic change in their distribution is thought to produce milder clinical manifestations of APSGN.

Thongboonkerd et al¹⁸ suggested that fluoride attenuated the expression of *Streptococcus pyogenes* virulence factors and implicated in non-suppurative complications of *S. pyogenes*, such as glomerulonephritis and rheumatic fever. In South Korea, fluoridation has been implemented in some small cities. However, larger metropolitan cities, such as Seoul, have not yet implemented fluoridation due to different opinions and opposition within society. The effect of fluoridation on the virulence of *S. pyogenes* remains controversial in South Korea.

Despite the well-known characteristics of APSGN, the predictive factors associated with the severity of acute nephritic syndrome in children with APSGN have not yet been studied. Although there has been no report describing the relationship between serum C3 levels and severe clinical

features of APSGN, we found that the degree of decrease in serum C3 level was milder in children with APSGN in recent years. Moreover, we found that decreased serum C3 level was associated with a decreased rate of acute nephritic features, such as edema. Since we were not able to examine the strain of GAS, a less virulent strain of GAS or a strong immunity of the host might be involved in these changing patterns of APSGN in South Korea.

For the diagnosis of APSGN, the level of C3 is a very important blood biomarker with clinical characteristics associated with nephritic features. When patients with APSGN show any acute nephritic symptoms, prompt and proper management should be initiated as the disease can progress rapidly to severe complications, such as acute renal failure or posterior reversible encephalopathy syndrome (PRES)¹⁹. A C3 serologic test and chest X-ray may be simple, rapid, and reliable tools for detecting severe nephritic signs, such as pulmonary edema, with or without related nephritic symptoms. We also found that monitoring of the serum C3 levels should be implemented, especially for patients exhibiting nephritic features. This study showed that the more nephritic features the patients had, the lower their C3 levels. This may help clinicians to determine how the changing patterns of C3 levels could be correlated with the extent of clinical severity of APSGN, predictable prognosis, and the timing of intensive care unit treatment. Conservative management is still the treatment of choice for APSGN, but proper management to prevent secondary complications of acute nephritic symptoms (e.g., seizure or sudden blindness due to PRES by rapidly developing hypertension) should be considered depending on the duration of C3 recovery.

The present study had some limitations. Since this was a single-center study, collaboration and cooperation from multi-centers are needed. A relatively limited number of cases have been investigated for the analysis. Throat culture test for streptococcal infection is not routinely performed on hospital admission in South Korea. When pharyngotonsillitis is suspected, empirical antibiotics tend to be used frequently according to the judgment of the physician. Even if early antibiotic therapy for streptococcal infection does not completely eradicate the risk of APSGN²⁰, it can alleviate the disease course. However, the university hospital in this study is one of the largest hospitals in South Korea and has the largest population of APSGN patients. Although it is difficult to cor-

rectly elucidate why the severity of APSGN has decreased since 1998, we believe that all the conditions mentioned above, including the enhanced antibiotics, improved hygiene, better living environment, and increased economic state, have affected the clinical manifestations and outcomes of APSGN. Additionally, the year 1998 is considered a period of transition for South Korea from a developing country to a developed country. South Korea became a member of the Organization for Economic Cooperation and Development in December 1996.

Regarding the predictive factors for the severity of APSGN, a statistical link between C3 levels and severity of nephritic symptoms was suggested. It was only discovered when C3 was compared to patients with ≤ 2 vs. ≥ 3 nephritic symptoms, with a *p*-value of 0.044. Furthermore, C3 levels were correlated with ≥ 2 nephritic symptoms, but surprisingly, not with more severe involvement (≥ 3 features). In this multivariate analysis, covariates included Ig, ASO, and complement fractions, but not BUN, creatinine, or proteinuria; and no justification was provided for this choice. Although serum C3 level was not correlated with the characteristics of acute nephritic symptoms or signs except edema, our analysis showed that low levels of C3 could be a potentially useful biomarker in diagnosing and predicting the severity of APSGN. In patients with APSGN, it would also be notable to analyze C3a and C3b fragment formed by the cleavage of complement component 3 in the future.

We were not able to include the data after acute phase symptoms due to the retrospective nature of this study. Therefore, further research is needed to determine how many nephritic features affect renal prognosis or whether the poor renal outcome is caused by other medical issues, such as proteinuria, in patients with APSGN. As APSGN can rapidly lead to chronic kidney disease or ESRD, periodic long-term follow-up will be important, especially if proteinuria or hematuria persists in patients with APSGN²¹.

Conclusions

The present study revealed that the lower serum C3 levels decreased in patients with APSGN. Moreover, the greater number of nephritic symptoms the patients had, the more accurately the level of C3 was able to predict the disease severity of patients with APSGN. In line with this fact,

the severity of APSGN became milder in South Korea after 1998, which might be due to several factors, such as improved hygiene and antibiotics, as well as a relatively lower decrease in C3 levels in recent years.

Author's Contributions

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Data curation: Jae Il Shin, Rita Yu, Se Jin Park, Keum Hwa Lee, I Re Lee, Song Yi Han; **Formal analysis:** Jae Il Shin, Se Jin Park, Keum Hwa Lee; **Methodology:** Hyon Suk Kim; **Resources:** Jae Il Shin, Ji Hong Kim; **Supervision:** Jae Il Shin, Ji Hong Kim; **Visualization:** Kyoung Hee Han, Keum Hwa Lee; **Writing – original draft:** Jae Il Shin, Kyoung Hee Han, Seong Heon Kim, Lee Smith, Andreas Kronbichler; **Writing – review & editing:** Se Jin Park, Jae Il Shin, Keum Hwa Lee, Lee Smith, Andreas Kronbichler, Ji Hong Kim.

All authors have read and approved the final manuscript.

Compliance with Ethical Standards

The study protocol was approved by the Institutional Review Board of the Yonsei University Health System (IRB No. 4-2017-0728). Since the present study is a retrospective study, we were given exemption from collecting informed consents by the IRB, and personal identifiers were completely removed and the data were analyzed anonymously. Our study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments..

Conflict of Interests

The authors declare that they have no conflict of interests.

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