ORIGINAL ARTICLE

Clinical Manifestations, Pathological Correlations, Prognostic Factors, and Outcomes of Severe Acute Postinfectious Glomerulonephritis with Rapidly Progressive Glomerulonephritis in Children

Nattaphorn Hongsawong, MD[1], Songkiet Suwansirikul, MD[2], Wattana Chartapisak, MD[1]

[1] Division of Pediatric Nephrology, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [2] Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Objective: To describe clinical spectrum, as well as biochemical and histological factors that could predict severe presentations and renal outcomes among children with rapidly progressive glomerulonephritis (RPGN) due to postinfectious glomerulonephritis (PIGN).

Material and Methods: A retrospective cohort study was conducted at Chiang Mai University Hospital, Thailand between February 2008 and January 2018. Ninety-six pediatric patients with PIGN were recruited. Clinical presentations, disease courses, laboratory data, renal histopathology, treatment, and outcomes were analyzed. Compare clinical manifestation and outcome between the two groups.

Results: The median age (interquartile range, IQR) was 11 (8 to 13) years with a male-to-female ratio of 1.8:1. RPGN was identified in 51.04% (49/96 patients). PIGN children with RPGN exhibited a higher prevalence of nephrotic range proteinuria (69.4% versus 53.2%, p=0.04), nephrotic syndrome (46.9% versus 17%, p=0.002), and hypoalbuminemia (81.3% versus 53.8%, p<0.0001) compared with those without RPGN. Multivariate analysis revealed that anuria, and hypoalbuminemia were predicting factors of RPGN [odd ratios 0.07 (95% CI 0.01 to 0.77), p=0.03 and 0.23 (95% CI 0.08 to 0.69), p=0.006, respectively]. Follow-up data were available among 78 patients (81.3%) with a median follow-up time of 762 (256.3 to 1,293) days. Complete remission was identified in all of PIGN without RPGN but only 71.4% in the RPGN group. Kaplan-Meier analysis revealed that patients with RPGN had a longer recovery time of generalized edema at 14 days (95% CI 12 to 15.9) versus 9 days (95% CI 7 to 12), p=0.023; proteinuria at 16 weeks (95% CI 11 to 20.8) versus 8 weeks (95% CI 4.25 to 15.75), p<0.0001; and impaired glomerular filtration rate (GFR) of nine weeks (95% CI 4.8 to 13.2) versus two weeks (95% CI 1 to 8), p=0.003. Subgroup analysis of prognostic factors of PIGN with RPGN revealed that high BMI z-score and kidney replacement therapy (KRT) requirement were associated with poor renal outcomes.

Conclusion: Hypoalbuminemia and anuria were predictive factors of RPGN in PIGN. High BMI z-score and low GFR required acute KRT were predictive factors of poor renal outcomes.

Keywords: Postinfectious glomerulonephritis; Acute post streptococcal glomerulonephritis; Rapidly progressive glomerulonephritis; Children

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Postinfectious glomerulonephritis (PIGN), a common type of reactive immune-mediated glomerulonephritis among children, develops following an infection. The spectrum of clinical features of acute PIGN ranges from asymptomatic microscopic hematuria to serious nephritis namely rapidly progressive glomerulonephritis (RPGN). The diagnosis is based on clinical manifestations and laboratory features. Renal biopsy is not indicated in typically presenting cases, however, may be required in those with unusual presentations or clinical courses, such as RPGN, persistent proteinuria, or prolonged hypocomplementemia. The prognosis is generally good in typical cases of PIGN[(1)]. Despite severe manifestations and acute kidney injury (AKI) requiring acute kidney replacement therapy (KRT), the majority of patients achieve complete remission without complications or long-term sequelae. However, a small number of patients develop complicated presentations such as RPGN resulting in AKI and hospitalization[(1)]. Some patients experience a lengthy course of symptoms or exhibit

Correspondence to:

Chartapisak W.

Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

Phone: +66-53-936462, **Fax**: +66-53-936461

Email: Wattana.c@cmu.ac.th

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persistent hypertension, proteinuria, chronic kidney disease (CKD), or progress to end-stage kidney disease (ESKD). In a small sample-sized cohort study, most children with PIGN-derived RPGN in Thailand have a favorable prognosis without any specific immunosuppressive therapy with more than 90% recovering normal kidney function at short-term follow-up, and a CKD risk of up to 31%[2]. Therefore, the present study aimed to describe the clinical manifestations, pathological findings, and prognostic characteristics of pediatric patients with PIGN causing RPGN. It is also to determine the associated factors of RPGN and poor outcomes among children with PIGN.

Materials and Methods

Study population

The present study was a single-center retrospective cohort analysis conducted at Chiang Mai University Hospital, Thailand. Ninety-seven patients with an age of onset less than 15 years, admitted with a diagnosis of PIGN between February 2008 and January 2018 were included. PIGN was defined by acute glomerulonephritis with hematuria or proteinuria plus one of the followings, (i) transient decrease of serum C_3 level or hypocomplementemia, (ii) evidence of the previous infection within a certain time, and (iii) compatible pathological findings with PIGN. Patients with persistently low C_3 after eight weeks of follow-up, and clinical or histological features revealing evidence of pre-existing renal diseases, such as IgA nephropathy and lupus nephritis, were excluded. The patients were divided into two groups according to the estimated glomerular filtration rate (eGFR) as PIGN with and without RPGN. RPGN was defined clinically by a decline of eGFR of 50% or more over three months or less. In children who did not have a baseline eGFR, the authors assumed a normal glomerular filtration rate (GFR) of 120 mL/minute/1.73 m^2.

Data collection

Medical charts were reviewed to collect data including basic demographic information, clinical course, laboratory investigations, renal pathology (if available), treatment modalities, and outcomes. Blood pressure (BP) was obtained from a mean of three different measurements from an oscillometer. Diagnosis of hypertension was done using the 2017 guidelines[3]. The hypertensive crisis was defined as systolic and diastolic BP greater than ninety-fifth percentile + 30 mmHg or stage 2 hypertension with acute end-organ damage. Hypertensive encephalopathy was defined as a hypertensive crisis with acute neurological symptoms including alteration of consciousness, headache, visual disturbance, seizures, or neurological deficits. Demographic data and anthropometric measurements including body weight, height, and body mass index (BMI) were collected. The WHO AnthroPlus Programs (version 2009) was used to calculate a BMI z-score and height for age z-score.The presence of fluid overload was defined as a minimum of 10% increase in body weight from baseline. Anemia was defined as hemoglobin or hematocrit greater than 2 standard deviations below the mean for age. Anti-streptolysin O (ASO) titer greater than 200 IU/mL, serum potassium greater than 5.5 mEq/L, serum sodium of less than 135 mEq/L, C_3 level of less than 550 µg/mL, C_4 level of less than 100 µg/mL, and serum albumin of less than 3.0 g/dL were defined as abnormal or positive findings. Significant proteinuria was defined as spot urine protein/creatinine ratio (UPCR) greater than 0.2 or 4 to 40 mg/m^2/hour on a 24-hour urine collection. Nephrotic range proteinuria was identified when spot UPCR greater than 2 or 40 mg/m^2/hour on a 24-hour urine collection. The eGFR based on serum creatinine before and after 2013 was calculated using the original Schwartz height-based formula[4] and the revised Schwartz equation[5], respectively. eGFR was computed based on serum creatinine at the time of initial admission when creatinine was highest to identify RPGN and at a period of more than three months at follow-up. An eGFR of less than 90 mL/minute/1.73 m^2 would be considered a renal impairment.

Histopathology examination was performed using standard techniques. Diffuse crescentic glomerulonephritis (CGN) was defined by crescents involving at least 50% of glomeruli. Electron microscopy (EM) was not performed as it was not available at the authors' site.

After hospital discharge, the patients were regularly followed every one to three months. Complete recovery was defined as the absence of proteinuria, a normal C_3 level and an eGFR of more than 90 mL/minute/1.73 m^2 without hypertension. Incomplete recovery was defined as persistent hypertension or CKD. CKD was diagnosed based on the GFR category from the 2012 guidelines[6]. For each patient, the end of the follow-up period was either disease resolution or death.

To identify the prognostic factors of incomplete recovery response in a group of children with

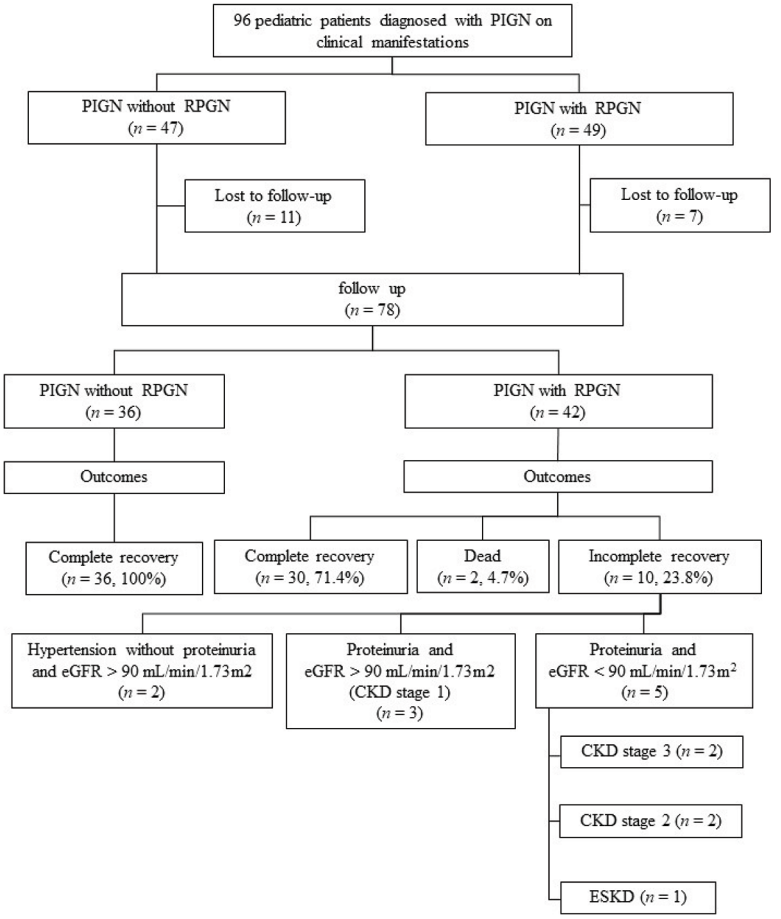


Figure 1. Pediatric patients with PIGN recruitment and follow-up flow diagram.

CKD=chronic kidney disease; ESKD=end-stage kidney disease; eGFR=estimated glomerular filtration rate; PIGN=post-infectious glomerulonephritis; RPGN=rapidly progressive glomerulonephritis

PIGN exhibiting RPGN, subgroup analysis was performed. The authors categorized them into two groups, complete and incomplete recovery groups. The aforementioned clinical data were compared to demonstrate the effects of these clinical features on outcomes.

Permission to obtain the data was granted by the Research Ethics Committee of Chiang Mai University Hospital. (Research ID: 5013).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). For descriptive statistics, categorical variables were reported as numbers and percentages; and continuous variables were reported as mean ± standard deviation or median (interquartile range, IQR), depending on data distributions. The categorical variables were compared with the chi-square test. Continuous variables were evaluated using the Student's t-test or the Mann-Whitney U test, where appropriate. Binary logistic regression was used to assess for any association between RPGN and poor clinical outcomes. Survival analyses were estimated using Kaplan-Meier methods. Time-zero for the time-to-event analysis was the onset of the disease. Differences between groups were assessed using the two-sided log-rank test. Cox regression analysis was performed to identify factors associated with the patient's survival. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics

Ninety-six children with PIGN were included in the present study. The median age of pediatric patients with PIGN was 11 (8 to 13) years and a range of 4 to 15 years, with a male-to-female ratio

Table 1. Clinical features of pediatric patients with PIGN and PIGN with RPGN

Clinical features	PIGN (n=47)	PIGN with RPGN (n=49)	Total (n=96)	p-value
Age (years); median (IQR)	10.25 (7.92 to 13.25)	12.20 (8.75 to 13.00)	11.08 (8.00 to 13.00)	0.33
Sex; n (%)				0.047
Male	35 (74.5)	27 (55.1)	62 (64.6)	
Female	12 (25.5)	22 (44.0)	34 (35.4)	
Fluid overload; n (%)	22 (46.8)	24 (50.0)	46 (48.4)	0.76
Height z-score; mean±SD	−0.86±1.19	−0.42±1.47	−0.63±1.36	0.11
BMI z-score; mean±SD	−0.22±1.60	−0.15±1.82	−0.18±1.70	0.84
Infection and latent period				0.59
Acute pharyngitis; n (%)	15 (31.9)	13 (26.5)	29 (29.2)	
Latent times (days); median (IQR)	7 (7.0 to 12.0)	9.5 (7.0 to 14.0)	7 (7.0 to 14.0)	
Skin infection; n (%)	12 (25.5)	10 (20.4)	22 (22.9)	
Latent times (days); median (IQR)	25.5 (14.0 to 30.0)	30.0 (14.0 to 37.5)	30.0 (14.0 to 30.0)	
Fever without localizing signs; n (%)	4 (8.5)	2 (4.1)	6 (6.3)	
Latent times (days); median (IQR)	13.5 (7.0 to 14.0)	5.0 (3.0)	10 (4.5 to 14.0)	
Other infections; n (%)	3 (6.4)	3 (6.1)	6 (6.3)	
Latent times (days); median (IQR)	14.0 (7.0)	7.0 (5.0)	7.0 (6.5 to 15.8)	
Unknown; n (%)	13 (27.7)	21 (42.9)	34 (35.4)	
Hypertension; n (%)				0.26
No	2 (4.3)	3 (6.1)	5 (5.2)	
Elevated blood pressure	1 (2.1)	4 (8.2)	5 (5.2)	
Stage 1 hypertension	3 (6.4)	7 (14.3)	10 (10.4)	
Stage 2 hypertension	41 (87.2)	36 (71.4)	77 (79.2)	
Hypertensive crisis; n (%)	21 (44.7)	18 (36.7)	39 (40.6)	0.43
Hypertensive encephalopathy; n (%)	7 (14.9)	6 (12.2)	13 (13.5)	0.71
Gross hematuria; n (%)	21 (44.7)	16 (32.7)	37 (38.5)	0.23
Edema; n (%)	45 (95.7)	46 (93.9)	91 (94.8)	0.68
Nephrotic syndrome; n (%)	8 (17.0)	23 (46.9)	31 (32.3)	0.002
Anuria; n (%)	1 (2.1)	16 (32.7)	17 (17.7)	<0.0001
Anemia; n (%)	40 (85.1)	41 (83.7)	81 (84.4)	0.85
Thrombocytopenia; n (%)	1 (2.1)	3 (6.1)	4 (4.2)	0.33
Urine protein creatinine ratio; median (IQR)	2.44 (0.85 to 5.27)	5.40 (2.25 to 10.97)	3.9 (1.60 to 7.75)	0.003
24-hour urine protein (mg/kg/day); median (IQR)	64.0 (22.47 to 114.13) (n=28)	84.94 (31.95 to 138.07) (n=34)	76.71 (31.95 to 131.77) (n=62)	0.24
Proteinuria; n (%)				0.04
No	5 (10.6)	0 (0.0)	5 (5.2)	
Significant proteinuria	17 (36.2)	15 (30.6)	32 (33.3)	
Nephrotic range proteinuria	25 (53.2)	34 (69.4)	59 (61.5)	
eGFR at initial time of admission (mL/minute/1.73 m^2); median (IQR)	80.02 (66.61 to 112.00)	26.15 (15.60 to 42.99)	57.16 (26.11 to 82.01)	<0.0001
The lowest eGFR on admission (mL/minute/1.73 m^2); median (IQR)	74.55 (62.15 to 101.81)	18.17 (12.80 to 31.18)	44.64 (17.78 to 74.50)	<0.0001
eGFR <90 mL/minute/1.73 m^2; n (%)	31(66)	49(100)	80 (83.3)	<0.0001
Sodium (mEq/L); mean±SD	139.52±4.18	136.35±4.59	137.91±4.65	0.001
Hyponatremia; n (%)	5 (10.6)	15 (30.6)	20 (20.8)	0.016
Potassium (mEq/L); mean±SD	4.33±0.75	4.80±0.80	4.57±0.81	0.004
Hyperkalemia; n (%)	7 (14.9)	19 (38.8)	26 (27.1)	0.008
ASO titer (IU/mL); median (IQR)	509.50 (295.50 to 769.0)	426.0 (255.0 to 800.0)	459 (288 to 775)	0.36
High ASO titer; n (%)	43 (91.5)	44 (91.7)	87 (91.6)	0.98
C_3 (µg/mL); median (IQR)	185.0 (173.0 to 257.0)	343.0 (173 to 765.25)	202 (173 to 465)	0.013
Low C_3; n (%)	42 (89.4)	33 (67.3)	75 (78.1)	0.009
Duration of complement examination from onset (days); median (IQR)	6.0 (4.0 to 12.0)	7.0 (4.0 to 13.5)	6.5 (4.0 to 12.75)	0.61
C_4 (µg/mL); mean±SD	187.52±57.79	238.58±106.68	213.85±89.62	0.022
Low C_4; n (%)	1 (3.2)	2 (6.1)	3 (4.7)	0.59
Serum albumin (g/dL); median (IQR)	3.1 (2.16 to 3.55)	2.49 (2.10 to 2.80)	2.7 (2.2 to 3.2)	<0.0001
Albumin status; n (%)				<0.0001
Normal (>3.0 g/dL)	25 (73.5)	9 (18.8)	34 (39.1)	
Hypoalbuminemia				
• 2.5 to 3.0 g/dL	10 (40)	15 (31.3)	25 (28.7)	
• <2.5 g/dL	4 (13.8)	24 (50.0)	28 (32.2)	
Steroid treatment; n (%)				<0.0001
No	41 (87.2)	18 (36.7)	59 (61.5)	
Oral prednisolone	6 (12.8)	4 (8.2)	10 (10.4)	
Pulse methylprednisolone	0 (0.0)	27 (55.1)	27 (28.1)	
Renal replacement therapy; n (%)	0 (0.0)	7 (14.3)	7 (7.3)	0.007
Other immunosuppressive drugs; n (%)	1 (2.1)	7 (14.3)	8 (8.3)	0.031
Follow-up duration (days); median (IQR)	790.50 (242.3 to 1482.3) (n=36)	639.00 (248.3 to 1219.25) (n=42)	762.0 (256.3 to 1293.00) (n=78)	0.62

PIGN=post-infectious glomerulonephritis; RPGN=rapidly progressive glomerulonephritis; SD=standard deviation; IQR=interquartile range; ASO=anti-streptolysin O; BMI=body mass index; C_3=complement 3 level; C_4=complement 4 level; eGFR=estimated glomerular filtration rate

Table 2. Predictors of severity presentation (RPGN) in PIGN children

Predictor	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	Adjusted p-value
Age (years)	1.09 (0.94 to 1.27)	0.25	1.22 (0.98 to 1.52)	0.07
Male	2.38 (1.01 to 5.64)	0.05	1.98 (0.59 to 6.73)	0.27
Anuria	0.05 (0.01 to 0.36)	0.003	0.07 (0.01 to 0.77)	0.03
Decreased C_3 level	4.07 (1.35 to 12.27)	0.013	2.52 (0.64 to 9.90)	0.18
Hyponatremia	0.27 (0.09 to 0.82)	0.02	0.28 (0.06 to 1.22)	0.09
Hyperkalemia	0.28 (0.10 to 0.74)	0.01	0.47 (0.11 to 2.00)	0.31
Hypoalbuminemia	0.13 (0.05 to 0.34)	<0.0001	0.23 (0.08 to 0.69)	0.006

CI=confidence interval; C_3=complement 3 level

Table 3. Predictors of outcomes of pediatric participants with PIGN and RPGN

Predictor	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	Adjusted p-value
BMI z-score	1.77 (1.06 to 2.94)	0.03	1.802 (1.013 to 3.206)	0.045
KRT	0.08 (0.01 to 0.90)	0.04	0.056 (0.004 to 0.769)	0.031
C_3	1.002 (1.000 to 1.004)	0.13	1.002 (1.000 to 1.004)	0.113

CI=confidence interval; BMI=body mass index; C_3=complement 3 level; KRT=kidney replacement therapy

of 1.82:1. RPGN was identified in 51.04% (49/96 patients) (Figure 1). The percentage of females in the RPGN group was significantly higher than the group without RPGN. The infections before PIGN diagnosis were identified in 64.7% of patients, with the most common infection being acute pharyngitis (29.2%). No difference was found in the types of preceding infections between PIGN with and without RPGN. Anuria was found in 17.7% of the patients, which was seen more frequently in the RPGN group (32% versus 2.1%, p<0.0001).

Laboratory examinations

Laboratory findings are listed in Table 1. Children in the RPGN group revealed a higher prevalence of nephrotic-range proteinuria (69.4% versus 53.2%, p=0.04) and nephrotic syndrome (46.9% versus 17%, p=0.002) in comparison with those without RPGN. Children in the RPGN group exhibited lower serum albumin (2.49 g/dL, IQR 2.10 to 2.80 versus 3.1 g/dL, IRQ 2.16 to 3.55, p<0.0001) and a higher proportion of hypoalbuminemia (81.3% versus 53.8%) than those without RPGN. Pearson's correlation test showed a positive correlation between serum albumin and eGFR (r=0.55, p<0.0001) and a negative correlation between UPCR and eGFR (r=–0.35, p=0.001). The median of eGFR at presentation was 57.16 (IRQ 26.11 to 82.01) mL/minute/1.73 m^2. More prevalence of hyponatremia and hyperkalemia were found among children with RPGN (p=0.016 and 0.004, respectively).

C_3 levels were evaluated in all patients, however, only 64 (66.67%) of them were tested for C_4 level. C_3 levels were normal in 21 patients (21.8%). Among these, 15 patients were diagnosed with PIGN based on renal biopsy. The rest of the patients presented with a history of infection with a range of latent periods of 7 to 30 days. They also had high ASO titer and complete recovery. C_3 and C_4 levels were found to be higher in the RPGN group compared with the other group (p=0.013 and 0.022, respectively). Moreover, the number of patients with a low C_3 level in the RPGN group was lower than those without RPGN (67.3% versus 89.4%, p=0.009). No correlation was observed between ASO titer and eGFR (r=0.13, p=0.23).

Predicting factors of RPGN at presentation

Multivariate analysis revealed that hypoalbuminemia and anuria at presentation were predicting factors of RPGN (Table 2).

Pathological findings in PIGN with RPGN

Twenty-nine of the studied children had available renal pathology data and completed follow-up (Figure 2). The most common histologic patterns of glomerular injury were diffuse endocapillary proliferative (72.4%) and exudative (93.1%) glomerulonephritis. Cellular and fibrocellular crescents were presented in 24.1% and 10.3% of patients, respectively. Interestingly, none of the RPGN patients had CGN. Patients with poorer outcomes displayed a higher percentage of glomerular segmental sclerosis, crescentic glomeruli, and exudative glomerulonephritis (Table 3).

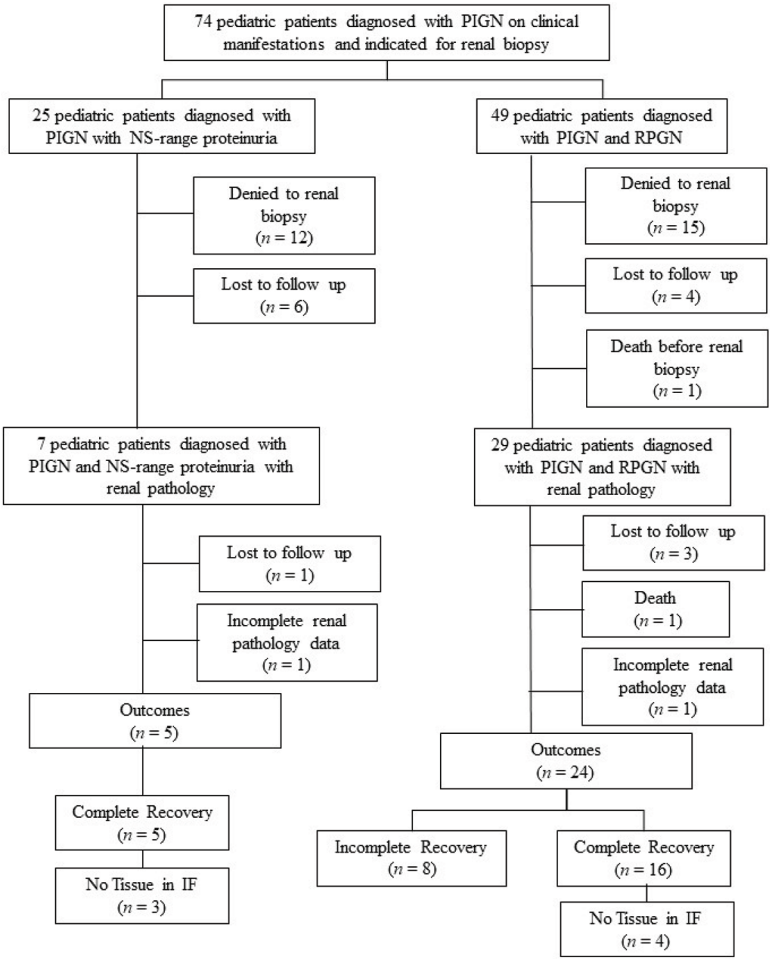


Figure 2. Renal biopsy in pediatric PIGN patients and follow-up flow diagram.

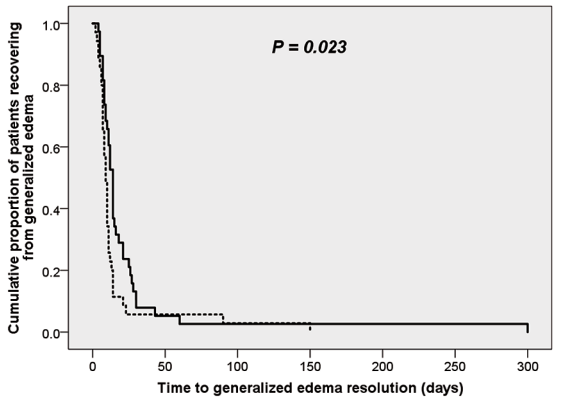
IF=immunofluorescence; NS=nephrotic syndrome; PIGN=post-infectious glomerulonephritis; RPGN=rapidly progressive glomerulonephritis

Glomeruli were sampled for immunofluorescence (IF) in all patients, unfortunately, no glomeruli were obtained in seven cases. The most common IF staining pattern was a diffuse global or segmental granular capillary loop, resembling a starry-sky appearance, seen in 81.8% of the 22 patients. The percentage of garland patterns in the incomplete recovery group seemed to be higher than that in the complete recovery group, however, no statistically significant difference was found (p=0.09). C_3 staining was the dominant immune reactant detected in the glomeruli in 90.8% of the patients, with a median staining intensity of 2+ (2 to 2), on a scale of 1 to 3+. Sole glomerular positivity for C_3 staining was detected in four patients (18.2%).

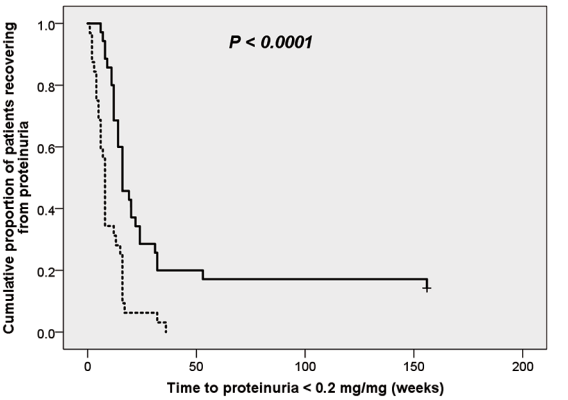
Treatment and outcomes

Acute KRT was indicated in 7.3% of all patients, and 14.3% of patients with RPGN. KRT, corticosteroids and other immunosuppressive therapies were more frequently required in children with RPGN (p=0.007, <0.0001, and 0.031, respectively).

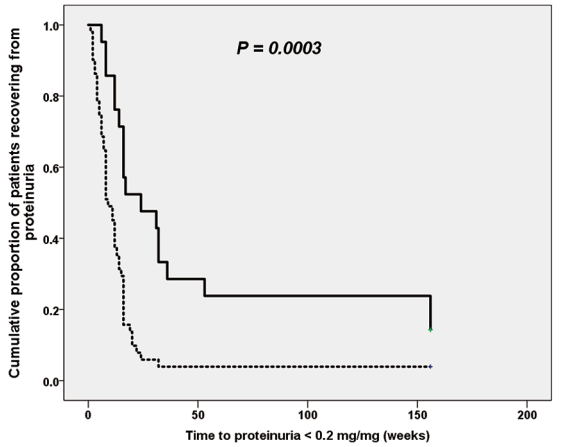
Follow-up data were available in 78 patients (81.3%). The overall median follow-up time was 762 (256.3 to 1,293) days. Sixty-six patients (84.6%) achieved complete recovery, ten patients (12.82%) had an incomplete recovery, with remaining hypertension (2.6%), persistent proteinuria with preserved GFR (3.85%), Stage 2 CKD (2.5%), Stage 3 CKD (2.5%). One patient (1.3%) progressed to ESKD requiring long-term KRT (Figure 1). Complete remission was observed in all cases of PIGN without RPGN and only 71.4% in the RPGN group. Two patients (4.7%) died during treatment, with one from *Pseudomonas* septicemia and the other from



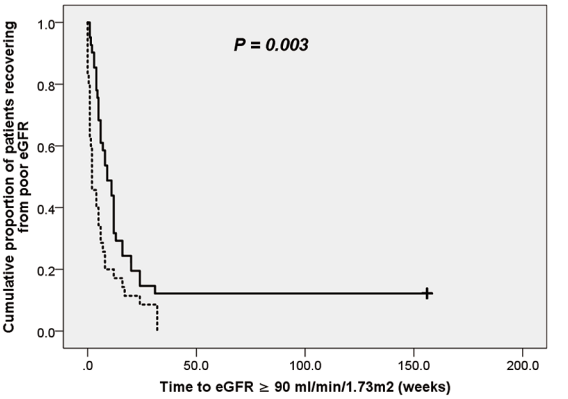
(a) Generalized edema was present in 96.05% of patients (35 with RPGN and 38 non-RPGN) and was prolonged in the RPGN group with a median (95% CI) time-to-resolution of 14 days (12.06 to 15.94) compared with 9 days (7.55 to 10.45) in the no-RPGN group (p=0.023). (The solid line represents children with PIGN with RPGN and the dashed line represents children with PIGN without RPGN.)



(b) The resolution rate of proteinuria determined by the Kaplan-Meier method was 92.5% overall, and 85.4% for the RPGN group. The median (95% CI) time-to-resolution of proteinuria in PIGN with RPGN was longer than in PIGN without RPGN 16 weeks (11.19 to 20.81) vs. 8 weeks (7.25 to 8.75), p<0.0001. (The solid line represents children with PIGN with RPGN and the dashed line represents children with PIGN without RPGN.)



(c) Resolution rate of proteinuria determined by the Kaplan-Meier method was 92.5% overall, and 81.8% for the NS group. The median (95% CI) time-to-resolution of proteinuria in PIGN with NS was longer than in PIGN without NS 24 weeks (1.57 to 46.43) vs. 9 weeks (6.50 to 11.50), p=0.0003. (The solid line represents children with PIGN with NS and the dashed line represents children with PIGN without NS.)



(d) Overall resolution rate of impaired eGFR was 93.4%, and 88% for patients with RPGN. The RPGN group required a longer time for eGFR to normalize (≥90 mL/minute/1.73 m^2), median (95% CI) time-to-normal eGFR 9 weeks (4.82 to 13.18) vs. 2 weeks (0 to 4.06), p=0.003. The solid line represents children with PIGN with RPGN and the dashed line represents children with PIGN without RPGN.

Figure 3. Kaplan Meier plot of remission rate of clinical outcomes in 79 PIGN children.

CI=confidence interval; eGFR=glomerular filtration rate; NS=nephrotic syndrome; PIGN=post-infectious glomerulonephritis; RPGN=rapidly progressive glomerulonephritis

α-streptococcal septicemia.

Univariate cox regression analyses showed low height z-score, high ASO titer, RPGN, high urine protein creatinine ratio, low serum albumin, and nephrotic syndrome were associated with the slow recovery of proteinuria. Regarding multivariate Cox regression analyses, RPGN and the nephrotic syndrome were independent prognostic factors [2.30 (95% CI 1.32 to 4.01), p=0.003 and 1.96 (95% CI 1.09 to 3.55), p=0.026, respectively] for the slow recovery of proteinuria. Univariate Cox regression analyses showed anuria, RPGN, high ASO titer, and low C_3 level were associated with the slow recovery of poor eGFR. According to multivariate Cox regression analyses, low C_3 level and RPGN were independent prognostic factors [0.99 (95% CI 0.99 to 1.00), p=0.046 and 1.93 (95% CI 1.16 to 3.21), p=0.011, respectively] for the slow recovery of impaired eGFR.

Using Kaplan-Meier analyses, patients without RPGN experienced a faster resolution of generalized edema (p=0.019), proteinuria (p<0.0001), and impaired eGFR (p=0.003) (Figure 3). While the time to recover from gross hematuria and low C_3 level

Table 4. Renal pathology of pediatric patients with PIGN compared cutcomes between complete remission and incomplete remission group

Renal pathological features in light microscope	Complete remission outcome (n=21)	Incomplete remission outcome (n=8)	Total (n=29)	p-value
Time to biopsy from onset of disease (days); median (IQR)	17 (8.0 to 32.0)	14.5 (10.25 to 28.75)	17.0 (9.0 to 30.0)	0.90
Crescentic involvement (%); median (IQR)	0 (0 to 0)	19.52 (3.5 to 33.1)	0 (0 to 16.9)	0.007
Range	0 to 26.6	0 to 38.5	0 to 38.5	
Type of crescent; n (%)				0.008
No crescent	17 (81.5)	2 (25.2)	19 (65.5)	
Cellular crescent	2 (9.5)	5 (62.5)	7 (24.1)	
Fibro cellular crescent	2 (9.5)	1 (12.5)	3 (10.3)	
Fibrous crescent	0 (0.0)	0 (0.0)	0 (0.0)	
Endocapillary proliferation; n (%)				0.90
No	4 (19.0)	1 (12.5)	5 (17.2)	
Focal	2 (9.5)	1 (12.5)	3 (10.3)	
Diffuse	15 (71.4)	6 (75.2)	21 (72.4)	
Endocapillary proliferation (%); median (IQR)	100 (54 to 100)	100 (35.5 to 100)	100 (54 to 100)	0.91
Circulating leukocyte; n (%)				0.05
No	1 (4.8)	1 (12.5)	2 (6.9)	
Mild	10 (47.6)	0 (0.0)	10 (34.5)	
Moderate	10 (47.6)	7 (87.5)	17 (58.6)	
Mesangial cells proliferation; n (%)				0.92
No	2 (9.5)	1 (12.5)	3 (10.3)	
Mild	12 (57.1)	5 (62.5)	17 (58.6)	
Moderate	6 (28.6)	2 (25.0)	8 (27.6)	
Severe	1 (4.8)	0 (0.0)	1 (3.4)	
Increased mesangial matrix; n (%)				0.59
No	7 (33.3)	4 (50.0)	11 (37.9)	
Mild	8 (37.1)	3 (37.5)	11 (37.9)	
Moderate	6 (28.6)	1 (12.5)	7 (24.1)	
Glomerulosclerosis (%); median (IQR)	0 (0 to 0)	4.15 (0 to 72.79)	0 (0 to 0)	0.08
Glomerular global sclerosis (%); median (IQR)	0 (0 to 0)	0 (0 to 13.64)	0 (0 to 0)	0.43
Glomerular segmental sclerosis (%); median (IQR)	0 (0 to 0)	4.15 (0 to 47.90)	0 (0 to 0)	0.05
Tubular atrophy (%); median (IQR)	0 (0 to 0)	0 (0 to 7.5)	0 (0 to 0)	0.32
Interstitial fibrosis (%); median (IQR)	0 (0 to 0)	0 (0 to 5)	0 (0 to 0)	0.32
IgG staining; n (%)				0.40
No	4 (28.6)	2 (25.3)	6 (27.3)	
1+	5 (35.7)	1 (12.5)	6 (27.3)	
2+	5 (35.7)	5 (62.5)	10 (45.5)	
C_3 staining; n (%)				0.83
No	2 (14.3)	0 (0.0)	2 (9.1)	
1+	1 (7.1)	0 (0.0)	1 (4.5)	
2+	10 (71.4)	6 (75.0)	16 (72.7)	
3+	1 (7.1)	2 (25.0)	3 (13.6)	
C_3 staining without IgG staining; n (%)	2 (14.3)	2 (25.0)	4 (18.2)	0.60
Pattern of IgG and/or C_3 staining; n (%)				0.09
No staining	2 (14.3)	0 (0.0)	2 (9.1)	
Granular or starry sky pattern	12 (85.7)	6 (75.0)	18 (81.8)	
Garland pattern	0 (0.0)	2 (25.0)	2 (9.1)	

IQR=interquartile range; C_3=complement 3 level; IgG=immunoglobulin G

Table 5. Clinical features of pediatric PIGN patients with RPGN comparing complete remission and incomplete remission group

Clinical features	Complete remission group (n=30)	Incomplete remission group (n=10)	p-value
Age (years); median (IQR)	12.21 (8.0 to 13.04)	12.0 (8.87 to 12.94)	0.56
Sex; n (%)			0.46
Male	17 (56.7)	7 (70.0)	
Female	13 (43.3)	3 (30.0)	
Height z-score; median (IQR)	–0.81 (–1.82 to 0.07)	0.60 (0.28 to 1.62)	0.005
BMI z-score; mean±SD	–0.42±1.42	1.27±2.47	0.011
Hypertensive crisis; n (%)	8 (26.7)	6 (60.0)	0.056
Hypertensive encephalopathy; n (%)	3 (10.0)	0 (0.0)	0.298
Fluid overload; n (%)	13 (43.3)	7 (70.0)	0.14
Edema; n (%)	29 (96.7)	9 (90.0)	0.402
Anemia for age; n (%)	25 (83.3)	8 (80.0)	0.810
Gross hematuria; n (%)	9 (30.0)	5 (50.0)	0.251
Urine protein creatinine ratio; median (IQR)	4.41 (1.84 to 10.99)	7.60 (2.40 to 11.46)	0.54
Proteinuria; n (%)			0.33
No	0 (0.0)	0 (0.0)	
Significant proteinuria	11(36.7)	2 (20.0)	
Nephrotic range proteinuria	19 (63.3)	8 (80.0)	
Nephrotic syndrome; n (%)	12 (40.0)	5 (50.0)	0.58
eGFR (mL/minute/1.73 m^2); median (IQR)	31.14 (17.46 to 51.16)	12.95 (6.79 to 33.25)	0.031
Anuria; n (%)	7 (23.3)	6 (60.0)	0.032
Serum albumin (g/dL); mean±SD	2.61±0.56	2.49±0.59	0.49
Serum ASO titer (IU/mL); median (IQR)	400 (248.25 to 535.75)	511.00 (302.50 to 910.25)	0.334
High ASO titer; n (%)	27 (93.1)	9 (90.0)	0.751
C_3 (µg/mL); median (IQR)	238.00 (172.50 to 598.75)	504.00 (266.5 to 869.25)	0.089
Low C_3; n (%)	22 (73.3)	6 (60.0)	0.43
C4 (µg/mL); mean±SD	209.0±79.79 (n=18)	310.3±87.64 (n=9)	0.006
Low C_4; n (%)	1 (5.6)	0 (0.0)	0.47
Kidney replacement therapy; n (%)	1 (3.3)	3 (30.0)	0.015
Steroid treatment; n (%)			0.83
No	12 (40.0)	3 (30.0)	
Oral prednisolone	2 (6.7)	1 (10.0)	
Pulse methylprednisolone	16 (53.3)	6 (60.0)	
Other immunosuppressive treatment; n (%)	3 (10.0)	1 (10.0)	1.00

SD=standard deviation; IQR=interquartile range; ASO=anti-streptolysin O; BMI=body mass index; C_3=complement 3 level; C_4=complement 4 level; eGFR=estimated glomerular filtration rate

was not different between the RPGN and non-RPGN groups [12 days (95% CI 8.33 to 15.67) versus 11 days (7.33 to 14.67), p=0.42 and 6 weeks (95% CI 4.97 to 7.03) versus 6 weeks (95% CI 4.51 to 7.50), p=0.53 respectively].

Microscopic hematuria in the RPGN group seemed to last longer than non-RPGN group with a median time-to-resolution of 10 (7 to 13.5) months versus 7.5 (4 to 12) months, however, no statistically significant difference was found (p=0.052). According to Kaplan-Meier analyses, patients without nephrotic syndrome experienced a faster resolution of proteinuria (p=0.0003) (Figure 3).

Prognostic factors of PIGN with RPGN

Subgroup univariate analyses demonstrated that high height z-score, high BMI z-score, high platelet, poor eGFR at the onset, higher C_4, anuria, and KRT requirement were associated with incomplete recovery or poor outcomes (Table 4). Multivariate analysis revealed that high BMI z-score and patients requiring KRT were associated with poor clinical response in PIGN with RPGN (Table 5).

Discussion

To the best of the authors' knowledge, the present study constituted the first retrospective

cohort study to describe short-term outcomes and prognostic factors of PIGN with RPGN in pediatric patients from Thailand, where this disease is still a major cause of RPGN[2]. In the present study, RPGN at the presentation of PIGN can be predicted by hypoalbuminemia and anuria at the onset. PIGN with RPGN patients may require more time to recover from generalized edema, proteinuria, and renal dysfunction. A high BMI z-score, renal impairment requiring KRT, and the percentage of glomerular crescents and segmental sclerosis on renal histopathology were associated with persistent proteinuria or CKD among pediatric patients experiencing PIGN with RPGN.

In the present study, the median age and the male-to-female ratio were similar to those previously reported in the literature[7]. The percentage of patients presenting with generalized edema, gross hematuria, and hypertension was also similar to a previous study[8]. Hypertensive crisis and hypertensive encephalopathy occurred in a higher proportion than in a recent report[9]. The percentages of patients with nephrotic-range proteinuria, hypoalbuminemia, and low eGFR were higher than those in developed countries but comparable to the data from developing countries or during epidemics[10,11]. Moreover, although severe clinical manifestations such as nephrotic syndrome or RPGN are not common, these can be found in most developing countries[10] or during epidemics[11].

Patients with PIGN presenting with RPGN displayed higher percentages of anuria, hyponatremia, hyperkalemia, hypoalbuminemia, nephrotic-range proteinuria, and nephrotic syndrome than patients without RPGN. The present study demonstrated a correlation between the presence of hypoalbuminemia/proteinuria and decreased eGFR, which was similar to findings from a previous study[12]. Demircioglu Kilic et al. postulated that hypoalbuminemia may be one of the predictors of decreased eGFR[12] because albumin maintains oncotic pressure and acts as an antioxidant during inflammation[13]. The type of the previous infection was not associated with the risk of developing RPGN in PIGN. These results are consistent with related literature[14]. Takeno et al. and Wong et al. found a positive relationship between high ASO titer and the severity of PIGN. They implied that patients with high ASO titer consequently developed an excessive immune response to streptococci resulting in severe symptoms[14]. On the contrary, the present study demonstrated that ASO titer was not different between patients with and without RPGN. Moreover, ASO titer did not correlate with eGFR. In the present study, only about 30% of patients presented with pharyngitis as a preceding infection. ASO titer is higher in pharyngitis-associated PIGN than in pyoderma-associated PIGN[15]. Some patients showed negative test results for ASO while anti-DNase and anti-hyaluronidase were positive[16]. Therefore, the association between ASO titer and the severity of the disease needs to be further clarified.

The morbidity and mortality rates of PIGN remain high in developing countries[10]. The present study reported the an overall complete remission rate of 84.6%, which was similar to 81.5% to 92% in Europe[17]. The complete recovery rate of 71.4% in PIGN with RPGN was comparable to 73.1% in north Ethiopia[18]. The mortality rate of 2.56% of PIGN in the present study was slightly lower than that from the northern Ethiopian report (5.9%)[18], whereas in Iran, no mortality or progression to CKD was found among children with PIGN[19].

Recently published literature has indicated that the persistence of hypertension and nephrotic-range proteinuria during the convalescence period are major indicators of long-term renal dysfunction[20]. The present study disclosed that children with PIGN-related RPGN sustained a long period of generalized edema, persistent proteinuria, and low eGFR. Sethi et al. defined atypical PIGN as having a longer period of improvement in persistent hematuria and proteinuria, progression to ESKD, or the presence of specific pathological features of PIGN with or without a preceding infection[21]. In the present study, the authors identified persistent proteinuria or CKD as so-called atypical PIGN, in 23.8% of PIGN with RPGN patients. Studies also identified that the majority of patients with atypical PIGN, had an underlying abnormality of the alternative pathway of complement regulation[21] that led to significant overlap with C_3 glomerulopathy (C_3GN). C_3GN could appear after the preceding infection[22]. Treating C_3GN might require immunosuppressant therapy, and the prognosis was unfavorable[23]. Al-Ghaiti et al. reported that 24.2% of cases with previous PIGN diagnoses were reclassified as having C_3GN based on IF and EM findings[22]. They found that children with biopsy features of atypical PIGN presented more severely at initial manifestations, and had lower C_3 levels than those observed in the C_3GN group. On the other hand, patients with C_3GN features had milder but more progressive disease, and 62.5% continued to have proteinuria or persistently low C_3 levels. They

proposed that the C_3 level at disease onset was not a predictive factor for outcome. However, due to a small sample size in this related study, the hypothesis remains unproven[24]. In the present study, children with PIGN-related RPGN had higher C_3 levels than those without RPGN. Children with PIGN with persistent proteinuria had higher C_3 levels than those who achieved a complete recovery. Subgroup analysis concerning outcomes of children suffering from PIGN with RPGN demonstrated lower C_3 level in the complete recovery group, however, no statistical significance was noted. Further studies with a large sample size might empower this possibility.

The other predicting factor of poor outcomes was low creatinine clearance requiring acute supportive KRT. This result was similar to a finding from another previous study. Wong et al. revealed that 66% of patients with PIGN requiring acute dialysis at disease onset tended to have persistent proteinuria that progressed to CKD[25].

One of the related studies could not determine statistical significance in the association between obesity and poor recovery in PIGN. However, they concluded that overweight/obese children appeared to have a greater residual renal injury after PIGN and required a longer time to achieve full recovery of urinary abnormalities compared with children who had normal BMI[26]. In the present study, a high BMI z-score was one the of predicting factors for incomplete recovery outcome of PIGN with RPGN. Many studies elucidated an association between numerous oxidative markers with obesity[27] because these inflammatory cytokines originated from adipocytes[28]. They hypothesized that obese patients, acquiring an inflammatory or immune-related disease, such as PIGN, may experience more extensive tissue injury leading to greater long-term sequelae[26]. Moreover, volume status evaluation and management in severely overweight patients are more challenging. Intensive fluid restriction among obese patients can aggravate persisting AKI from pre-renal azotemia resulting in greater time to renal recovery.

Renal biopsy was performed in 29 patients with an indication of RPGN. None of them exhibited diffuse crescents. In severe cases, the epithelial focal segmental crescent was the most common finding, while a diffuse crescent, so-called CGN, was rare[29]. RPGN could stem from glomerular hypercellularity, giving rise to the narrowing of the capillary lumen, which correlated with low GFR[30]. Several studies have indicated that crescentic lesions in over 40% of glomeruli, global glomerulosclerosis, and interstitial fibrosis correlated with poor kidney outcomes or progression to ESKD[20]. On the contrary, a small study demonstrated no significant relationship between biopsy score and clinical course including the need for acute dialysis, duration of dialysis, creatinine at onset, presence of anuria and nephrotic-range proteinuria[25]. The number of glomerular crescents and glomerular segmental sclerosis were associated with incomplete kidney recovery in the present study. The chronic lesions seen by LM may have resulted from progressive glomerular injury from a persistent alternative complement pathway dysregulation, sequelae from acute glomerulonephritis, or a maladaptive focal segmental glomerulosclerosis resulting from obesity-related glomerulopathy.

C_3GN is defined as a dominant C_3 IF staining and lack of other significant immunoglobulins, whereas in PIGN, bright staining of both C_3 and IgG are noted. In the present study, isolated C_3 accumulation shown in IF was not a predictive factor for poor prognosis. The timing of renal biopsy may affect the deposition of C_3 and IgG. The early renal biopsy lesions in C_3GN are similar to PIGN. Likewise, PIGN sometimes shows isolated C_3 deposition without IgG, particularly during the post-acute phase[21]. Moreover, IgG may not be present in atypical PIGN. IF alone cannot differentiate these two conditions from each other. Finding subepithelial hump-like basement membrane deposits in the EM might play an important role to distinguish PIGN from C_3GN[24]. However, the presence of a "hump" is not specified in only PIGN but can also be seen in C_3GN[31]. Interestingly, recent reports have postulated the later development of PIGN to chronic C_3GN by repeat biopsies[32]. Due to the lack of EM in the present study, children with isolated C_3 accumulation could have been either PIGN, atypical PIGN, or C_3GN. EM study and investigation of alternative pathways of complement might help to classify patients as mentioned or they could indicate a transformation from glomerular injuries triggered by infection to C_3GN.

The current study encountered limitations concerning retrospective data collection. Firstly, the center is a tertiary public hospital, hence, these results may not be generalizable to the entire country. Secondly, C_4 level and renal histopathology were not available in some cases. EM was also unavailable in the present study. Finally, the present study employed a relatively short follow-up period with some patients lost to follow-up.

Conclusion

Hypoalbuminemia was a predictive factor of RPGN at presentation in PIGN. The prognosis of children with PIGN remains excellent. Severe complications, especially RPGN and nephrotic syndrome, are still common in Thailand. High BMI z-score, low GFR requiring acute KRT, the percentage of glomerular crescents and glomerular segmental sclerosis on renal pathology are predictive factors of poor renal outcomes including persistent proteinuria and CKD. EM and testing of alternative pathway dysregulation might help to distinguish typical PIGN, atypical PIGN, and C_3G, and might help to initiate early treatment to achieve an improved outcome.

What is already known on this topic?

The prognosis of children with PIGN with RPGN was excellent. Low GFR requiring acute KRT and chronic change in renal pathology are predictive factors of developing chronic kidney disease.

What this study adds?

This study describes short-term outcomes of PIGN with RPGN in pediatric patients in Thailand. The results of this study aid in the knowledge of the risk factors of severe presentation such as RPGN and poor renal outcome of pediatric patients with PIGN.

Conflicts of interest

All authors declare no competing interests.

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