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Hypertension/prehypertension and its determinants in pediatric IgA nephropathy

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Abstract

Immunoglobulin A nephropathy (IgAN) is a major cause of secondary hypertension (HT) of renal origin – a significant prognostic factor of IgAN. In children, similar to HT, prehypertension (pre-HT) is becoming a significant health issue. However, the role of secondary HT and pre-HT (HT/pre-HT) in the progression of pediatric IgAN remains unclear. We investigated the effects of HT/pre-HT on prognosis and its determinants as well as their correlation with clinicopathological parameters to identify more effective therapeutic targets.

This single-center retrospective study compared clinicopathological features and treatment outcomes between patients with and without HT/pre-HT in 108 children with IgAN. Independent risk factors for HT/pre-HT were evaluated; segmental glomerulosclerosis was a significant variable, whose relationship with clinicopathological parameters was analyzed.

Clinical outcomes of patients with and without HT/pre-HT differed considerably ($P = .006$) on ≥6 months follow-up. Patients with HT/pre-HT reached complete remission less frequently than those without HT/pre-HT ($P = .014$). Age, serum creatinine, prothrombin time, and segmental glomerulosclerosis or adhesion were independent risk factors for HT/pre-HT in pediatric IgAN ($P = .012$, $P = .017$, $P = .002$, and $P = .016$, respectively). Segmental glomerulosclerosis or adhesion was most closely associated with glomerular crescents ($r = 0.456$, $P < .01$), followed by Lees grades ($r = 0.454$, $P < .01$), renal arteriolar wall thickening ($r = 0.337$, $P < .01$), and endocapillary hypercellularity ($r = 0.306$, $P = .001$). The intensity of IgA deposits, an important marker of pathogenetic activity in IgAN, was significantly associated with the intensity and location of fibrinogen deposits (intensity: $r = 0.291$, $P = .002$; location: $r = 0.275$, $P = .004$).

HT/pre-HT in pediatric IgAN patients is an important modifiable factor. A relationship is observed between HT/pre-HT and its determinants, especially segmental glomerulosclerosis. Potential therapeutic approaches for IgAN with HT/pre-HT might be directed toward the management of coagulation status, active lesions, and hemodynamics for slowing disease progression.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, APTT = activated partial thromboplastin time, ARBs = angiotensin receptor blockers, BP = blood pressure, CCBs = calcium channel blockers, CKD = chronic kidney disease, DBP = diastolic blood pressure, DHP = dihydropyridine, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, FDP = fibrinogen degradation products, HT = hypertension, HT/pre-HT = HT and pre-HT, IF = immunofluorescence, IgAN = Immunoglobulin A nephropathy, KDOQI = Kidney Disease Outcomes Quality Initiative, MAP = mean arterial pressure, NAG = N-acetyl-beta-D-acetyl-glucosaminidase, PP = pulse pressure, pre-HT = prehypertension, PT = prothrombin time, SBP = systolic blood pressure, SCr = serum creatinine, SG = specific gravity, SOsm = serum osmolality, UOsm = urine osmolality.

Keywords: children, hypertension, Immunoglobulin A nephropathy, prehypertension, segmental glomerulosclerosis

1. Introduction

Immunoglobulin A nephropathy (IgAN), the most common primary glomerular disease worldwide in adults and children, is mesangial proliferative glomerulonephritis characterized by predominant mesangial IgA deposits. Initially considered a benign condition, IgAN is increasingly recognized as a form of glomerulonephritis with progressive potential. The long-term prognosis of IgAN substantially varies among individuals; whereas some patients have only asymptomatic microscopic hematuria for many years, up to 40% of patients progress to end-stage renal disease (ESRD), necessitating renal replacement treatment (dialysis or kidney transplantation) within 10 to 20 years after a renal biopsy.[1] A growing number of studies have identified the prognostic value of clinicopathological characteristics in patients with IgAN. Besides renal lesion-related parameters such as severe proteinuria, impaired renal function, and advanced histopathological findings at the time of diagnosis, hypertension (HT) is an independent risk factor for IgAN progression and a strong predictor of poor prognosis.[2] Children with chronic kidney disease (CKD), unlike adults, most often present with secondary HT, as blood pressure (BP) elevation

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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predominantly is a sequela of CKD[3] – that is, secondary HT is a common consequence of renal damage and decreased renal function.[4] However, there are very limited data on secondary HT, and even lesser data on prehypertension (pre-HT), in the pediatric population. Our preliminary study found that secondary HT and pre-HT (HT/pre-HT) were observed in children with IgAN,[5] although the factors that are independently associated with HT/pre-HT are not known. CKD-associated HT/pre-HT needs to be controlled to prevent significant renal deterioration and excessive cardiovascular morbidity and mortality. Therefore, in this study, we aimed to investigate the risk factors for renal HT/pre-HT in pediatric patients with IgAN and identify more effective therapeutic targets to facilitate early intervention.

2. Materials and methods

2.1. Patients

This study retrospectively included 108 pediatric patients with renal biopsy-proven IgAN, diagnosed at our center from 2006 to 2013; the diagnostic criterion of IgAN was the predominant deposition of IgA immune complexes in the glomerular mesangium without evidence of systemic disease. BP was measured by the auscultatory method in the right upper arm with a sphygmomanometer (Jiangsu Yuyue Medical Equipment & Supply Co., Ltd.; size: 350 mm × 92 mm × 50 mm) using a standard protocol.[6] BP measurements were recorded on 3 consecutive days after admission We disregarded the first measure and the average of the second and third BP measurements was recorded as the patients BP. Both pre-HT (systolic blood pressure [SBP]/diastolic blood pressure [DBP] ≥120/80 mmHg) and HT (SBP/DBP ≥140/90 mm Hg) were defined using the age-, gender-, and height-specific BP percentile algorithm recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004 Working Group[7] (Patients were classified as those with HT/pre-HT (HT/pre-HT group) and without HT/pre-HT (non-HT/pre-HT group) for a comparative analysis in this study. The study protocol was approved by the institutional review board of the Beidaihe Rehabilitation and Recuperation Center of PLA (approval no. 20130136). Informed consent, for the use of clinical or pathologic data in future studies, was obtained from a parent or legal guardian of each patient at the time of the renal biopsy. Children with other secondary forms of HT were excluded from the study. Exclusion criteria included renal parenchymal abnormalities (polycystic renal disease, multicystic dysplastic renal disease, hydronephrosis, and chronic pyelonephritis), renovascular abnormalities (renal artery stenosis or thrombosis, and renal vein thrombosis), iatrogenic causes (corticosteroids, decongestants, and caffeine), childhood tumors associated with hypertension (Wilms tumor, neuroblastoma and pheochromo cytoma), as well as endocrinopathies associated with HT (hypercortisolism, hyperthyroidism, hyperaldosteronism, diabetes and congenital adrenal hyperplasia[8])

2.2. Patient assessment

Clinical and laboratory data including sex, age, and initial BP were collected at the time of renal biopsy from IgAN patients. Clinical signs of IgAN included: isolated hematuria (macroscopic and microscopic hematuria), isolated proteinuria (24-hours urine protein <50 mg/kg), hematuria and proteinuria (24-hours urine protein <50 mg/kg), acute glomerulonephritis (characterized by abrupt onset of hematuria which is often accompanied by proteinuria, HT, edema, and azotemia with a short latency period of less than 3 months), nephrotic syndrome, rapidly progressive glomerulonephritis, and chronic glomerulonephritis (characterized by persistent hematuria and/or proteinuria for more than 3 months with or without edema, HT and long-term progression of renal dysfunction).[9] We collected laboratory data on

1. urinary specific gravity (SG), urinary N-acetyl-beta-D-acetylglucosaminidase (NAG), urine osmolality (UOsm), and urinary fibrin/fibrinogen degradation products (FDP);
2. serum creatinine (SCr), uric acid, serum calcium, immunoglobulin, complement, total cholesterol, serum osmolality (SOsm), and serum FDP;
3. platelet count; coagulation function (prothrombin time [PT], activated partial thromboplastin time [APTT], and fibrinogen); and
4. the estimated glomerular filtration rate (eGFR; calculated according to the updated Schwartz formula).[10]

Patients were classified into 4 stages by eGFR according to 2002 Kidney Disease Outcomes Quality Initiative (KDOQI) guideline criteria,[11] these being: CKD stage 1 (eGFR≥ 90 ml/minutes per 1.73 m^2); CKD stage 2 (60 ml/minutes per 1.73 m^2≤ eGFR ≤89 ml/minutes per 1.73 m^2); CKD stage 3 (30 ml/minutes per 1.73 m^2≤ eGFR≤59 ml/minutes per 1.73 m^2); and CKD stage 4 (15 ml/minutes per 1.73 m^2≤ eGFR ≤29 ml/minutes per 1.73 m^2).

2.3. Renal histopathology

Renal biopsies were processed routinely for direct immunofluorescence and light microscopy according to the standard protocol.[12,13] For immunofluorescence microscopy, we used fluorescein isothiocyanate-conjugated polyclonal rabbit/goat anti-human antibodies for IgA, IgG, IgM, C3, C4, Clq, and fibrinogen (Zhongshan Goldenbridge Biotechnology Co. Ltd, Beijing, China). Fluorescence intensity was semi-quantitatively graded on a scale of 0 to 3+ (0, negative; 1+, weak staining; 2+, moderate staining; and 3+, strong staining). Paraffin sections were stained with hematoxylin and eosin, Masson trichrome, periodic acid-Schiff, and periodic acid silver methenamine for light microscopic examination. All biopsy slides were re-reviewed by 2 pathologists blinded to the patients' clinical data. Biopsies were graded by Lees grades[14] and the Oxford MEST-C scores (mesangial hypercellularity, M; endocapillary hypercellularity, E; segmental glomerulosclerosis or adhesion, S; tubular atrophy/interstitial fibrosis, T; and glomerular crescents, C).[15]

2.4. Treatment and response evaluation

To evaluate therapeutic management and patient response, we collected prescriptions from the patients during follow-up. Prescriptions included agents for renin–angiotensin–aldosterone system blockade (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]), dihydropyridine (DHP)-calcium channel blockers (CCBs), α1/β1-adrenergic receptor blockers, corticosteroids, other immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, and lefunomide), and antithrombotics (antiplatelet drugs, anticoagulants, and thrombolytics).

We used the following definitions for outcomes analysis. *complete remission*: normal urine, BP, and renal function at follow-up; *partial remission*: asymptomatic hematuria and/or proteinuria (proteinuria <1 g/day) as well as the absence of peripheral edema, HT, and renal dysfunction at follow-up; *progression of CKD*: an increase in proteinuria (proteinuria ≥1 g/day) and/or uncontrolled HT and/or elevated SCr level (SCr <442 μmol/L); and *ESRD*: elevated SCr ≥442 μmol/L.[16]

2.5. Treatment protocol

The treatment protocol of the study is provided in Supplementary Table 1, http://links.lww.com/MD/E892. We considered corticosteroid therapy in patients with persistent proteinuria ≥1 g/d after supportive therapy for >3 months. The patients with nephrotic syndrome or a relative amount of crescents, as well as an acute tubulointerstitial lesion on a kidney biopsy, might consider adding corticosteroid directly. Immunosuppressors were considered if patients presented with persistent nephrotic syndrome or significant crescent formation (cyclophosphamide, mycophenolate mofetil, and leflunomid), or progressive decline in renal function (cyclophosphamide) after corticosteroid therapy. Immunosuppressors (leflunomide) were considered alone if the patients with persistent proteinuria ≥1 g/d refused the use of corticosteroid because of poor response depending on the patients intention. Initially, patients used prednisone (0.8–1 mg/kg. d; maximum, 60 mg/d) for 2 months, which was tapered to 5 mg every 2 weeks and stopped within 6 to 8 months. Another regimen of corticosteroid therapy was high-dose intravenous methylprednisolone pulse therapy (500 or 250 mg/d for 3 successive days, partially repeated 3 times within 3 weeks), which was determined by the treating physician, followed by a standard dose of prednisone. Overall, more patients with nephrotic syndrome required intensive immunosuppressive therapy compared with patients with non-nephrotic syndrome. Furthermore, other medications (ACEIs or ARBs, DHP-type CCBs, α1/β1-adrenergic receptor blockers, diuretics, antithrombotics, and other drugs to promote blood circulation and clear blood stasis) were determined by the treating physician. All patients were followed up for 6 months or longer. All medications used during the study period were recorded.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (minimum-maximum) and were compared using an independent sample *t*-test or Mann–Whitney *U* test. Categorical variables are expressed as frequencies with percentages, and were compared using the Chi-Squared test, Mann–Whitney *U* test, or Kruskal–Wallis test. Univariate and multivariate logistic regression analyses were conducted to determine risk factors for HT/pre-HT in patients with IgAN. Results were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). Correlations were tested by Spearmans correlation coefficient. $P < .05$ was considered indicative of statistically significant differences. Statistical analyses were undertaken in SPSS 12.0 (Chicago, IL, USA).

3. Results

3.1. Clinical presentation

There were 73 boys and 35 girls with an overall mean age of 12.57 ± 3.01 years. Of the 108 patients enrolled in this study, 48 patients (44.44%) had the nephrotic syndrome, 32 (29.63%) had hematuria, and proteinuria (proteinuria <50 mg/kg), and 16 (14.81%) had chronic glomerulonephritis at the time of renal biopsy. Patients with isolated hematuria (8.33%), isolated proteinuria (1.85%), and acute glomerulonephritis (0.93%) constituted only a minor proportion of our study population. No patient had rapidly progressive glomerulonephritis. We found HT/pre-HT as an initial sign of IgAN in 21 of 108 (19.44%) patients; moreover, nephrotic syndrome was present in 42.86% and 44.83% of patients with and without HT/pre-HT, respectively. The hematuria–proteinuria sign was reported in 38.10% and 27.59% of patients with and without HT/pre-HT, respectively. Apart from these patients, 19.05% and 13.79% of patients with and without HT/pre-HT, respectively, had chronic glomerulonephritis. However, the between-group differences in presenting symptoms were not significant for the HT/pre-HT and non-HT/pre-HT groups ($P = .297$, Table 1).

3.2. Treatments and outcomes

In the follow-up period lasting 6 months or longer (range 6–140 months), 27 patients (HT/pre-HT: 4 [3.70%], non-HT/pre-HT: 23 [21.30%]) were lost to follow-up. Both HT/pre-HT and non-HT/pre-HT patients received similar treatments – corticosteroids and immunosuppressive agents, renin-angiotensin system blockers, ACEIs or ARBs, diuretics, and antithrombotics/drugs to promote blood circulation and clear blood stasis. We observed a significant difference in the prescription of DHP-CCBs (11.76% vs 0 for HT/pre-HT and non-HT/pre-HT, respectively, $P = .011$) and α1/β1-adrenergic receptor blockers (35.29% vs 0, for HT/pre-HT and non-HT/pre-HT, respectively, $P < .01$). In the follow-up period, 13 of 17 (76.47%) patients with HT/pre-HT had remission (complete remission: 2 [11.76%], partial remission: 11 [64.71%]). Four of 17 (23.53%) patients progressed from CKD to ESRD. In the non-HT/pre-HT group (n = 64), 57 (89.06%) patients had remission (complete remission: 31 [48.44%], partial remission: 26 [40.63%]), but 7 (10.94%) patients had CKD progression to ESRD. Patients in the non-HT/pre-HT group had complete remission more often than those in the HT/pre-HT group ($P = .014$, Table 2). Treatment characteristics of IgAN patients with HT and pre-HT are provided in Table 3.

3.3. Risk factors for HT/pre-HT

The baseline clinical and pathological features are provided in Supplementary Table 2, http://links.lww.com/MD/E893 and

Table 1

Clinical presentation at the time of renal biopsy in IgAN patients with and without HT/pre-HT.

Clinical presentation*	HT/pre-HT	non-HT/pre-HT
Isolated hematuria, n (%)	0 (0.00)	9 (10.34)
Isolated proteinuria, n (%)	0 (0.00)	2 (2.30)
Hematuria and proteinuria, n (%)	8 (38.10)	24 (27.59)
Acute glomerulonephritis, n (%)	0 (0.00)	1 (1.15)
Nephrotic syndrome, n (%)	9 (42.86)	39 (44.83)
Chronic glomerulonephritis, n (%)	4 (19.05)	12 (13.79)

* Clinical terms are defined in the Methods section.

Chi-Squared test: $\chi^2 = 6.091$, $P = .297$.

IgAN = immunoglobulin A nephropathy, HT = hypertension, pre-HT = prehypertension, HT/pre-HT = HT and pre-HT.

Table 2

Treatment characteristics, clinical outcomes and remission duration of IgAN patients with and without HT/pre-HT.

	HT/pre-HT (n = 17)	non-HT/pre-HT (n = 64)	*P* value
Treatments, n (%)			
Corticosteroids and immunosuppressive therapy	13/17 (76.47)	42/64 (65.63)	.576
Corticosteroids alone	4/17 (23.53)	14/64 (21.88)	1.000
Corticosteroids plus immunosuppressors	8/17 (47.06)	26/64 (40.63)	.633
Immunosuppressors alone	1/17 (5.88)	2/64 (3.13)	1.000
ACEIs or ARBs	5/17 (29.41)	8/64 (12.50)	.091
DHP-type CCBs	2/17 (11.76)	0/64 (0.00)	.011
α1/β1-adrenergic receptor blockers	6/17 (35.29)	0/64 (0.00)	<0.01
α1-adrenergic receptor blockers	1/17 (5.88)	0/64 (0.00)	.075
β1-adrenergic receptor blockers	5/17 (29.41)	0/64 (0.00)	<.01
Diuretics	5/17 (29.41)	15/64 (23.44)	.612
Antithrombotics	10/17 (58.82)	31/64 (48.44)	.446
Other drugs to promote blood circulation and clear blood stasis	7/17 (41.18)	33/64 (51.56)	.446
Clinical outcomes*, n (%)			.006
Complete remission	2/17 (11.76)	31/64 (48.44)	.014
Partial remission	11/17 (64.71)	26/64 (40.63)	.076
Progression of CKD	3/17 (17.65)	7/64 (10.94)	.739
ESRD	1/17 (5.88)	0/64 (0.00)	.075
Remission duration, months			
Complete remission	55 (16-94)	46 (6–140)	1.000
Partial remission	15 (6–67)	29.50 (6–128)	.366

* Clinical terms are defined in the Methods section.

IgAN = Immunoglobulin A nephropathy, HT = hypertension, pre-HT = prehypertension, HT/pre-HT = HT and pre-HT, ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, DHP = dihydropyridine, CCBs = calcium-channel blockers, CKD = chronic kidney disease, ESRD = end-stage renal disease.

Supplementary Table 3, http://links.lww.com/MD/E894 respectively. On univariate logistic regression analysis, age, SCr, eGFR, lower CKD stage, uric acid, PT, SOsm, UOsm, urinary SG, and the presence of M1, S1, T1/T2, C1/C2, and renal arteriolar wall thickening were significantly associated with HT/pre-HT. Multiple logistic regression analysis identified age (OR 1.937, 95% CI 1.157–3.244, $P = .012$), SCr (OR 1.018, 95% CI 1.003–1.033, $P = .017$), PT (OR 0.348, 95% CI 0.181–0.672, $P = .002$), and S1 (OR 13.630, 95% CI 1.637–113.502, $P = .016$) remained independent risk factors for IgAN with HT/pre-HT (Table 4). Compared to the non-HT/pre-HT group, patients with HT/pre-HT presented with higher age (14.67 ± 2.37 vs 12.07 ± 2.94, $P < .01$), lower PT (11.85 ± 1.14 vs 13.11 ± 1.57, $P = .001$), higher SCr (67 [range 31–356] vs 50 [range 26–227], $P = .001$), and a higher percentage of segmental glomerulosclerosis or adhesion (47.62% vs 18.39%, $P = .005$) (Fig. 1).

3.4. Clinicopathological features in patients with and without segmental glomerulosclerosis or adhesion

We found IgG deposition in glomeruli in 9 of the 82 patients (S0) but in none of the 26 patients (S1) ($P = .022$, Table 5). Compared with patients who had S0, those with S1 had a higher proportion of intense IgA deposits (13 [50.00%] vs 24 [29.27%] for IgA 3+, $P = .040$, Table 5). Fifty one (62.20%), 27 (32.93%), and 4

Table 3

Treatment characteristics of IgAN patients with HT and pre-HT.

	HT (n = 4)	pre-HT (n = 13)	*P* value
Treatments, n (%)			
Corticosteroids and immunosuppressive therapy	4/4 (100.00)	9/13 (69.23)	.114
Corticosteroids alone	1/4 (25.00)	3/13 (23.08)	.937
Corticosteroids plus immunosuppressors	2/4 (50.00)	6/13 (46.15)	.893
Immunosuppressors alone	1/4 (25.00)	0/13 (0.00)	.078
ACEIs or ARBs	2/4 (50.00)	3/13 (23.08)	.316
DHP-type CCBs	2/4 (50.00)	0/13 (0.00)	.009
α1/β1-adrenergic receptor blockers	2/4 (50.00)	4/13 (30.77)	.488
α1-adrenergic receptor blockers	1/4 (25.00)	0/13 (0.00)	.078
β1-adrenergic receptor blockers	1/4 (25.00)	4/13 (30.77)	.823
Diuretics	2/4 (50.00)	3/13 (23.08)	.316
Antithrombotics	3/4 (75.00)	7/13 (53.85)	.442
Other drugs to promote blood circulation and clear blood stasis	1/4 (25.00)	6/13 (46.15)	.442

IgAN = Immunoglobulin A nephropathy, HT = hypertension, pre-HT = prehypertension, HT/pre-HT = HT and pre-HT, ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, DHP = dihydropyridine, CCBs = calcium-channel blockers.

Table 4

Univariate and multivariate analyses of independent risk factors for HT/pre-HT in patients with IgAN.

	Univariate regression analysis		Multivariate regression analysis	
	ORs (95% CIs)	*P*-value	ORs (95% CIs)	*P* value
Age (years)	1.527 (1.182–1.973)	.001	1.937 (1.157–3.244)	.012
Gender (male/female)	1.684 (0.562–5.045)	.352	–	–
Serum creatinine (μmol/L)	1.014 (1.000–1.027)	.043	1.018 (1.003–1.033)	.017
eGFR (mL/min per 1.73 m^2)	0.978 (0.962–0.994)	.007	0.997 (0.904–1.099)	.952
CKD stage* (n)			–	–
CKD 2 vs CKD 1	0.162 (0.086–0.306)	<.01		
CKD 3+4 vs CKD 1	0.643 (0.278–1.485)	.301		
Uric acid (μmol/L)	1.010 (1.004–1.015)	.001	1.005 (0.994–1.016)	.389
PT (s)	0.551 (0.372–0.817)	.003	0.348 (0.181–0.672)	.002
APTT (s)	1.008 (0.961–1.058)	.745	–	–
Serum calcium (mmol/L)	0.029 (0.001–0.983)	.049	–	–
Total cholesterol (mmol/L)	0.960 (0.825–1.118)	.600	–	–
SOsm [mOsm/(kg. H_2O)]	1.059 (1.004–1.117)	.035	1.014 (0.969–1.061)	.554
UOsm [mOsm/(kg. H_2O)]	1.003 (1.000–1.006)	.041	1.001 (0.993–1.009)	.800
Urinary SG (n)				
≥1.020 vs ≥1.010	0.100 (0.013–0.781)	.028	0.988 (0.004–234.674)	.997
≥1.030 vs ≥1.010	0.161 (0.080–0.325)	<.01	0.197 (0.016–2.369)	.201
Urinary NAG (IU/mmolCr)	1.035 (0.999–1.072)	.058	–	–
Mesangial hypercellularity (n)	0.244 (0.152–0.393)	<.01	0.001 (0.000–938.509)	.317
M0 vs M1				
Endocapillary hypercellularity (n)	0.936 (0.360–2.432)	.892	–	–
E0 vs E1				
Segmental glomerulosclerosis or adhesion (n)	3.743 (1.367–10.248)	.010	13.630 (1.637–113.502)	.016
S0 vs S1				
Tubular atrophy/interstitial fibrosis (n)				
T0 vs T1	0.200 (0.119–0.337)	<.01	0.142 (0.000–351.961)	.624
T0 vs T2	2.000 (0.181–22.056)	.01	3.781 (0.001–26507.899)	.768
Glomerular crescents (n)				
C0 vs C1	0.204 (0.107–0.390)	<.01	0.004 (0.000–3250.897)	.429
C0 vs C2	0.333 (0.157–0.709)	.004	0.006 (0.000–5243.683)	.466
Renal arteriolar wall thickening (n)	3.710 (1.383–9.954)	.009	0.285 (0.010–7.960)	.460

* Clinical terms are defined in the Methods section.

HT = hypertension, pre-HT =prehypertension, HT/pre-HT = HT and pre-HT, IgAN = Immunoglobulin A nephropathy, ORs = odds ratios, 95% CIs = 95% confidence intervals, eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease, PT = prothrombin time, APTT = activated partial thromboplastin time, SOsm = serum osmolalities, UOsm = urine osmolalities, SG = specific gravity, NAG = N-acetyl-beta-D-acetyl-glucosaminidase.

(4.88%) patients with S0 were graded on Lees grades of IgAN as Grades I + II, Grade III, and Grades IV + V, respectively. Patients with S1 had a lower percentage of Grades I+II (11.54%) and a higher percentage of Grade III (65.38%) and Grades IV+V (23.08%) categorization, compared to patients with S0. Thus, Lees grades differed significantly between patients with S1 and S0 ($P<.01$, Fig. 2A). Compared to the S0 group, patients with S1 had significantly higher percentages of E and C lesions ($P=.001$ and $P<.01$, respectively, Fig. 2B and Fig. 2C) in 5 pathological variables (MEST-C). Patients with S1 had a higher prevalence of renal arteriolar wall thickening than those with S0 ($P<.01$, Fig. 2D).

3.5. Correlation of segmental glomerulosclerosis or adhesion and other pathological parameters

We did not find an association between IgG deposition and segmental glomerulosclerosis or adhesion ($P=.079$), while the association between intensity of IgA deposits and segmental glomerulosclerosis or adhesion was not considered due to low correlation coefficient ($r=0.199$). However, the underlying cause of segmental sclerosis or adhesion might be correlated with different histological features such as glomerular crescents ($r=0.456$, $P<.01$), Lees grades ($r=0.454$, $P<.01$), renal arteriolar wall thickening ($r=0.337$, $P<.01$), and endocapillary hypercellularity ($r=0.306$, $P=.001$) (Table 6).

3.6. Association of IgA deposition with coagulation variables

We used direct immunofluorescence (IF) to examine glomerular deposits of fibrinogen, and 50 of the 108 patients (46.30%) had high IF scores (1+, n=33; 2+, n=17). Fibrinogen was present in both the mesangium and glomerular capillary loops, but not exclusively in the mesangium (Table 7). This confirms that IgAN involves a coagulation process that leads to fibrin formation in the glomerulus.[17–19] Furthermore, the intensity of IgA deposits, an important marker of pathogenetic activity in IgAN, was significantly correlated with the intensity and location of fibrinogen deposits (intensity: $r=0.291$, $P=.002$; location: $r=0.275$, $P=.004$) (Table 8). The location of IgA deposits and the intensity or location of fibrinogen deposits were not significantly associated (Table 9).

4. Discussion

Compared to adults, there is a higher incidence of a secondary cause for HT in pediatric patients, and CKD is considered a

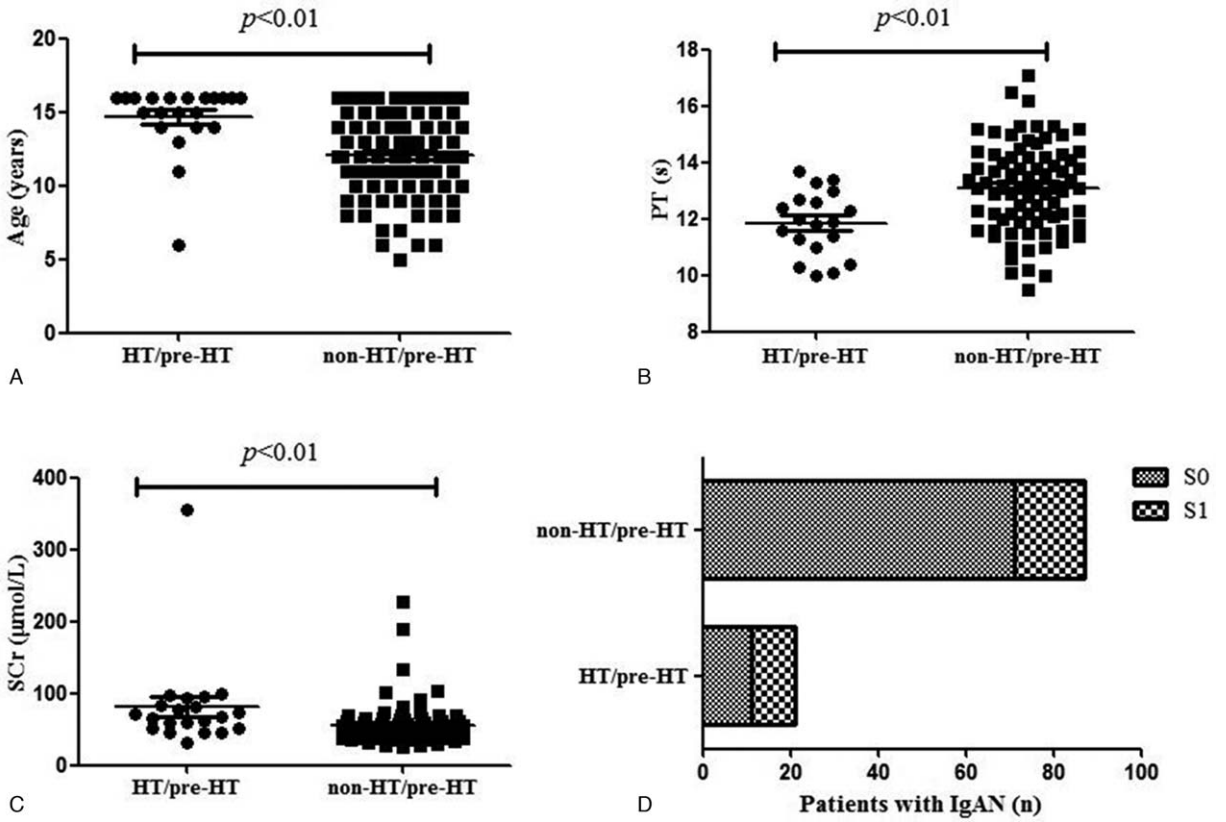

Figure 1. Independent risk factors for HT/pre-HT in patients with IgAN on univariate and multivariate logistic regression analyses. A. Age differences in HT/pre-HT versus non-HT/pre-HT (14.67 ± 2.37 vs 12.07 ± 2.94, $P < .01$). B. PT differences in HT/pre-HT versus non-HT/pre-HT (11.85 ± 1.14 vs 13.11 ± 1.57, $P = .001$). C. Differences in SCr in HT/pre-HT versus non-HT/pre-HT (67 [31–356] vs 50 [26–227], $P = .001$). D. Segmental glomerulosclerosis or adhesion in HT/pre-HT versus non-HT/pre-HT (47.62% vs 18.39%, $P = .005$). HT, hypertension; pre-HT, prehypertension; HT/pre-HT, HT and pre-HT; IgAN, Immunoglobulin A nephropathy; SCr, serum creatinine.

common cause of pediatric secondary HT.[20,21] CKD and HT are intimately connected, and synergistically induce a further decline in renal function.

Both HT and pre-HT are frequently underdiagnosed in the pediatric CKD population.[22] We found that 5 of the 21 patients with HT/pre-HT were not on antihypertensives, indicating that a proportion of these patients could be undiagnosed, especially those with pre-HT. This condition going undiagnosed could be attributed to a lack of adequate awareness of pre-HT. Furthermore, complete remission was more common in normotensive children compared to those with HT/pre-HT despite the absence of significant differences in clinical presentation between HT/pre-HT and non-HT/pre-HT; this suggests better short-term outcomes in the non-HT/pre-HT patients compared to those with HT/pre-HT. It was markedly apparent that HT/pre-HT secondary to IgAN significantly influenced the clinical prognosis of pediatric patients, even with regard to short-term outcomes. Therefore, it is imperative to emphasize HT/pre-HT at renal biopsy as an important indicator for treatment and renoprotection. Early diagnosis of elevated BP, especially through early recognition of pre-HT, will help formulate an intervention strategy, and improved BP control may slow the relentless progression of CKD.

We analyzed antihypertensive pharmacotherapy in patients with IgAN, and found significant between-group differences in the use of α1/β1-adrenergic receptor blockers and DHP-type CCBs in the HT/pre-HT and non-HT/pre-HT groups; however, there were no significant differences in ACEI, ARBs, or diuretic use. These results indirectly indicate that sympathetic overactivation and vasoconstriction may be more likely to be identified as important etiopathogenetic factors in secondary HT/pre-HT. We found that ACEIs/ARBs and diuretics were used very frequently, especially for the antiproteinuric and renoprotective efficacy of ACEIs/ARBs, even in non-HT/pre-HT patients.

Univariate analysis showed that many clinical and pathological elements were associated with HT/pre-HT. However, multivariate analysis found that only age, SCr, PT, and segmental glomerulosclerosis or adhesion maintained their independent association. PT served as the basis for therapy with antithrombotics and drugs to promote blood circulation and clear blood stasis. PT might be a potential therapeutic target for early intervention in IgAN patients, especially those with HT/pre-HT. Segmental glomerulosclerosis or adhesion is an adverse prognostic factor in the progression of IgAN[23]; however, its significance in secondary HT/pre-HT has not been elucidated yet. We verified segmental glomerulosclerosis or adhesion as a risk factor for HT/pre-HT in patients with IgAN, and it was the only histological factor independently associated with HT/pre-HT. Thus, we infer segmental glomerulosclerosis or adhesion, a common morphologic pattern of injury, plays a pivotal role in HT/pre-HT secondary to IgAN, and requires conservative management that aims for control of BP.

Table 5

Comparison of clinical and pathological features between patients with IgAN with and without segmental glomerulosclerosis or adhesion.

Clinicopathological features	S0	S1	*P* value
Number of patients	82	26	
Platelet ($\times 10^9$/L)	262.49 ± 82.49	248.08 ± 72.07	.426
PT (s)	12.99 ± 1.60	12.48 ± 1.45	.159
Fibrinogen (g/L)	3.33 ± 0.93	3.15 ± 0.61	.264
Urine FDP (μg/ml)	0.69 ± 0.88	0.89 ± 0.94	.360
Serum FDP (μg/ml)	5.73 (1.13–96)	4.95 (0.75–15)	.243
Serum IgA (g/L)	2.30 ± 1.18	2.53 ± 0.99	.375
Serum IgA/C3	1.70 (0.55–13.33)	2.17 (0.53–5.16)	.072
IgG deposition, n (%)	9 (10.98)	0 (0.00)	.022
IgA deposition, n (%)			.040
1+	15 (18.29)	2 (7.69)	
2+	43 (52.44)	11 (42.31)	
3+	24 (29.27)	13 (50.00)	
IgM deposition, n (%)	53 (64.63)	16 (61.54)	.775
C3 deposition, n (%)	54 (65.85)	19 (73.08)	.493
C4 deposition, n (%)	0 (0.00)	0 (0.00)	1.000
C1q deposition, n (%)	7 (8.54)	2 (7.69)	1.000
Fibrinogen deposition, n (%)	38 (46.34)	12 (46.15)	.987
IgM-C3 deposition, n (%)			.148
IgM-, C3-	8 (9.76)	5 (19.23)	
IgM-, C3 deposition	21 (25.61)	5 (19.23)	
IgM deposition, C3-	20 (24.39)	2 (7.69)	
IgM and C3 deposition	33 (40.24)	14 (53.85)	
IgG-C3 deposition, n (%)			.107
IgG-, C3-	27 (32.93)	7 (26.92)	
IgG-, C3 deposition	46 (56.10)	19 (73.08)	
IgG deposition, C3-	1 (1.22)	0 (0.00)	
IgG and C3 deposition	8 (9.76)	0 (0.00)	
Lee's grades, n (%)			< 01
Grades I + II	51 (62.20)	3 (11.54)	<.01
Grade III	27 (32.93)	17 (65.38)	.003
Grades IV + V	4 (4.88)	6 (23.08)	.016
Oxford classification			
Mesangial hypercellularity, n (%)			.457
M0	1 (1.22)	0 (0.00)	
M1	81 (98.78)	26 (100.00)	
Endocapillary hypercellularity, n (%)			.001
E0	45 (54.88)	5 (19.23)	
E1	37 (45.12)	21 (80.77)	
Tubular atrophy/interstitial fibrosis, n (%)			.135
T0	79 (96.34)	23 (88.46)	
T1	1 (1.22)	2 (7.69)	
T2	2 (2.44)	1 (3.85)	
Glomerular crescents, n (%)			<.01
C0	60 (73.17)	5 (19.23)	<.01
C1	18 (21.95)	18 (69.23)	<.01
C2	4 (4.88)	3 (11.54)	.456
Renal arteriolar wall thickening, n (%)	20 (24.39)	16 (61.54)	<.01

IgAN = Immunoglobulin A nephropathy, S = segmental glomerulosclerosis or adhesion, PT = prothrombin time, FDP = fibrin/fibrinogen degradation products.

Our study showed that the co-deposition of IgM was similar in patients with or without segmental glomerulosclerosis lesion, although primary focal segmental glomerulosclerosis was characterized by diffuse predominant mesangial IgM deposits. Segmental sclerosis or adhesion in IgAN, a chronic lesion on the new MEST-C score,[15] may occur as a consequence of distinct processes. We found segmental glomerulosclerosis or adhesion was associated with different histological features, including Lee's grades, endocapillary hypercellularity, glomerular crescents, and renal arteriolar wall thickening. Our findings support a variety of etiopathogenetic mechanisms for segmental glomerulosclerosis or adhesion, including sequelae of previously active lesions (endocapillary hypercellularity and glomerular crescents), and hemodynamic changes (renal arteriolar wall thickening).[24] Moreover, these observations may indicate targets for improving segmental glomerulosclerosis or adhesion. Active lesions or segmental sclerosis can be partially prevented by corticosteroid and/or immunosuppressive regimens, which help control secondary HT/pre-HT. Mesangial IgA deposits are the initiating event in the pathogenesis of IgAN; although IgM, IgG, and complement components are often co-deposited, they are not essential for disease activity or

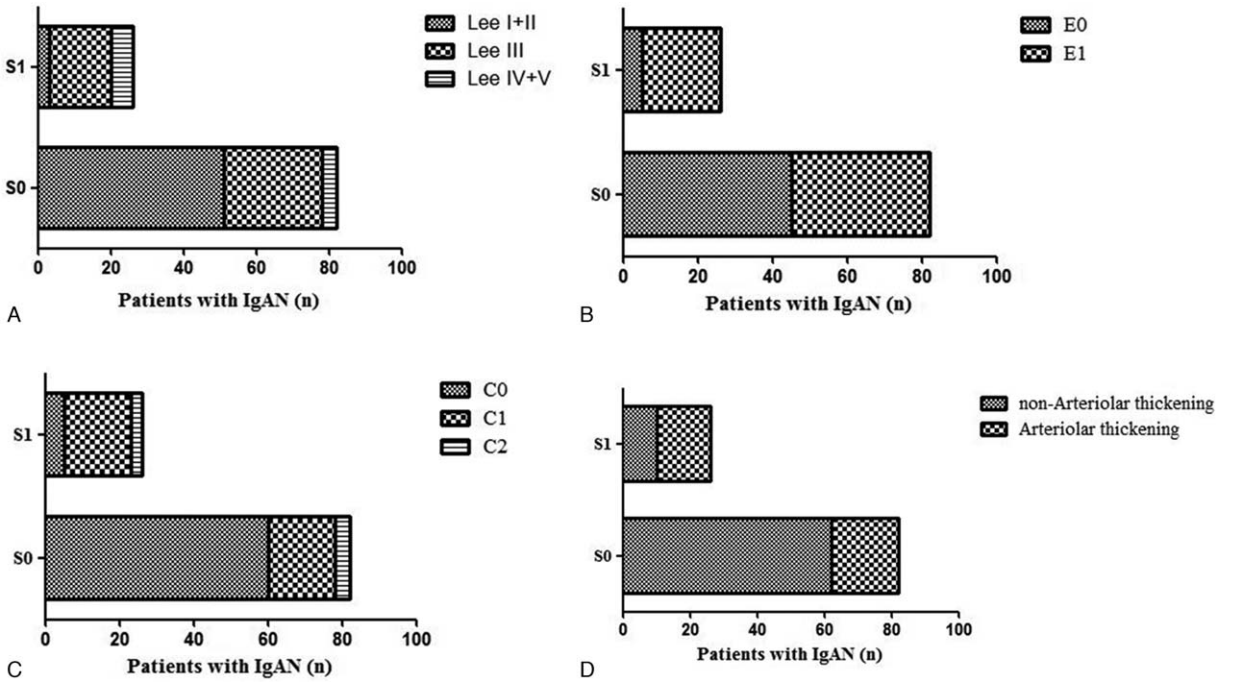

Figure 2. Factors associated with segmental glomerulosclerosis or adhesion in patients with IgAN on Spearman's correlation analyses. A. Lees grades in IgAN patients with and without segmental glomerulosclerosis or adhesion (S0 vs S1, $P < .01$: Grades I + II of S0 vs Grades I + II of S1, $P < .01$; Grade III of S0 vs Grade III of S1, $P = .003$; Grades IV + V of S0 vs Grades IV + V of S1, $P = .016$). B. Endocapillary hypercellularity in IgAN patients with and without segmental glomerulosclerosis or adhesion (S0 vs S1, $P = .001$). C. Glomerular crescents in IgAN patients with and without segmental glomerulosclerosis or adhesion (S0 vs S1, $P < .01$: C0 of S0 vs C0 of S1, $P < .01$; C1 of S0 vs C1 of S1, $P < .01$). D. Renal arteriolar wall thickening in IgAN patients with and without segmental glomerulosclerosis or adhesion (S0 vs S1, $P < .01$). IgAN = Immunoglobulin A nephropathy.

progression. Deposits of IgA alone seem adequate to provoke glomerular injury in susceptible individuals.[25] Moreover, we found that the intensity of IgA deposits had a significant positive association with the intensity and location of fibrinogen deposits. These observations potentially indicate that novel therapeutic targets in controlling secondary HT/pre-HT and slowing the progression of IgAN should not only focus on decreasing active lesions, but also on improving hemodynamics and coagulation status, together with decreasing IgA accumulation.

The main limitation of the present study is its retrospective observational nature, which precludes the establishment of a cause-effect relationship. Moreover, the study sample was relatively small and from a single center and had a short follow-up period, given the relentless silent progression of IgAN. Despite these limitations, the current study suggests important risk factors and new therapeutic targets for HT/pre-HT.

In conclusion, HT/pre-HT are frequently present in IgAN. Age, SCr, PT, and segmental glomerulosclerosis or adhesion are independent risk factors for IgAN with HT/pre-HT. Furthermore, segmental glomerulosclerosis or adhesion is associated with pathological findings, such as endocapillary hypercellularity, glomerular crescents, and renal arteriolar wall thickening. The intensity of IgA deposits was significantly associated with the intensity and location of fibrinogen deposits. We emphasize that potential therapeutic approaches for IgAN with HT/pre-HT might be directed toward the management of coagulation status, active lesions, and hemodynamics.

Table 6

Correlation of segmental glomerulosclerosis or adhesion and pathological features in patients with IgAN.

	Segmental glomerulosclerosis or adhesion	
	r	*P* value
Intensity of IgA deposits (n)	0.199	.039
IgG deposition (n)	−0.170	.079
Lee's grades (n)	0.454	<.01
Endocapillary hypercellularity (n)	0.306	.001
Glomerular crescents (n)	0.456	<.01
Renal arteriolar wall thickening (n)	0.337	<.01

IgAN = immunoglobulin A nephropathy.

Table 7

Association of intensity of IgA deposition with coagulation variables in patients with IgAN.

	Intensity of IgA deposits			
	1+	2+	3+	*P* value
Platelet ($\times 10^9$/L)	245.71 ± 53.74	255.09 ± 86.44	270.86 ± 80.61	.498
PT (s)	12.60 ± 1.64	12.94 ± 1.60	12.94 ± 1.58	.763
Fibrinogen (g/L)	3.11 ± 0.75	3.45 ± 0.85	3.10 ± 0.89	.129
Serum FDP (μg/ml)	6.82 ± 6.81	9.25 ± 12.59	11.91 ± 18.85	.464
Urine FDP (μg/ml)	0.84 ± 1.03	0.75 ± 0.92	0.66 ± 0.77	.809
Serum IgA/C3	2.40 ± 2.96	2.03 ± 1.04	1.97 ± 0.87	.579
Intensity of fibrinogen deposits, n (%)				.009
-	12 (11.11)	33 (30.56)	13 (12.04)	
1+	4 (3.70)	15 (13.89)	14 (12.96)	
2+	1 (0.93)	6 (5.56)	10 (9.26)	
Location of fibrinogen deposits, n (%)				.014
-	12 (11.11)	33 (30.56)	13 (12.04)	
Glomerular capillary loops	0 (0.00)	1 (0.93)	0 (0.00)	
Mesangium and glomerular capillary loops	5 (4.63)	20 (18.52)	24 (22.22)	

IgAN = immunoglobulin A nephropathy, PT = prothrombin time, FDP = fibrin/fibrinogen degradation products.

Table 8

Correlation between intensity of IgA deposits and fibrinogen deposits in patients with IgAN.

	Intensity of fibrinogen deposits Location of fibrinogen deposits			
	r	*P* value	*r*	*P* value
Intensity of IgA deposits	0.291	.002	0.275	.004

IgAN = immunoglobulin A nephropathy.

Table 9

Association of location of IgA deposition with fibrinogen deposits in patients with IgAN.

	Location of IgA deposits			
	Mesangium	Glomerular capillary loops	Mesangium and glomerular capillary loops	*P* value
Intensity of fibrinogen deposits, n (%)				.175
-	32 (29.63)	0 (0.00)	26 (24.07)	
1+	22 (20.37)	0 (0.00)	11 (10.19)	
2+	10 (9.26)	1 (0.93)	6 (5.56)	
Location of fibrinogen deposits, n (%)				.559
-	32 (29.63)	0 (0.00)	26 (24.07)	
Glomerular capillary loops	0 (0.00)	1 (0.93)	0 (0.00)	
Mesangium and glomerular capillary loops	32 (29.63)	0 (0.00)	17 (15.74)	

IgAN = immunoglobulin A nephropathy.

Author contributions

Qing-Ying Fu, Lu Ma, Chang-Chun Li and Zhi-Jun He conceived and designed research; Qing-Ying Fu, Lu Ma, Zhi-Jun He and Wei-Hua Wang collected data and conducted research; Qing-Ying Fu, Chang-Chun Li, Wei-Hua Wang and Kai-Fa Luo analyzed and interpreted data; Qing-Ying Fu, Lu Ma, Yang Liu and Zhi-Hao Zhang wrote the initial paper; Chang-Chun Li, Zai-Bo Yang, Hai-Lian Tang and Jun-Hui Yan revised the paper; Chang-Chun Li had primary responsibility for final content. All authors read and approved the final manuscript.

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