

Risk Factors for Renal Involvement in Childhood Henoch-Schonlein Purpura (IgA Vasculitis)

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ABSTRACT

This study was designed to investigate the risk factors for renal involvement in children with immunoglobulin A (IgA) vasculitis. It is a hospital-based retrospective cohort study with a sample size of 117 children aged ≤ 16 years with primary IgA vasculitis. Out of 117 patients, 49 (41.9%) developed renal injury. Univariate analysis revealed that age, gastrointestinal bleeding (GIB), time of duration, white blood cell count, D-dimer, and platelet count were all associated with renal injury in the patients with HSP. These variables were included in the multivariate logistic regression analysis. Results showed that elevated D-dimer level, older age, and GIB were independent risk factors for renal damage in patients with IgA vasculitis.

Key Words: Henoch-schonlein purpura, Immunoglobulin A vasculitis, Nephritis, D-dimer, Risk factors.

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Henoch-Schonlein Purpura (HSP), also known as immunoglobulin A (IgA) vasculitis, is a systemic immune complex-mediated aseptic necrotic disease of small vessels, which is commonly seen in children.¹ It can involve all systems of the body, the main manifestations are non-thrombocytopenic purpura, abdominal pain, arthritis, and kidney disease. Most children recover within weeks to months. Renal involvement is the key factor that determines the course of treatment and prognosis of IgA Vasculitis. About 40% of IgA vasculitis children develop haematuria and / or proteinuria within 4–6 weeks as symptoms of renal involvement. A small number of these patients eventually develop nephritic or nephrotic syndrome, which can affect their health for life.² Therefore, it is particularly important to evaluate the risk factors affecting kidney damage in children with IgA vasculitis.

From June 2018 to December 2020, 117 patients under the age of 16 years who were initially diagnosed with IgA vasculitis in the Department of Dermatology at the Affiliated Hospital of Medical University and had not received anticoagulant treatment were included in this study. The diagnosis for IgA vasculitis followed the European League Against Rheumatism / Pediatric Rheumatology International Trials Organisation / Pediatric Rheumatology European Society in 2010¹, include palpable purpura, abdominal pain, arthritis, renal involvement, and the pathological manifestations of leukocytoclastic vasculitis.

Patients who had primary or secondary renal diseases and underwent anticoagulant therapy within one month before the admission were excluded from the analysis; a history of surgery or trauma within the last month; proteinuria was defined as >150 mg protein/24 hours. Renal involvement was clinically diagnosed by proteinuria and/or haematuria.¹

Data analysis was carried out using IBM SPSS 26.0 statistical software. A probability plot was carried out on the data, independent t-test was used if it conformed to the positive distribution, otherwise, Mann-Whitney U tests were conducted. Chi-squared tests were performed to evaluate possible differences between the frequencies of categorical variables. Continuous variables were expressed as means, SDs, medians and IQRs while categorical variables were expressed as counts and percentages. Multivariate analysis was conducted by forward stepwise logistic regression. A value of $p < 0.05$ was defined as a significant difference.

The patient population consisted of 59 boys (50.4%) and 58 girls (49.6%). Kidney injury patient age was significantly higher than those without renal impairment (9.45 ± 2.96 years versus 7.6 ± 2.63 years, $p = 0.001$). In total, 49 (41.9%) patients developed renal injury within one year. Baseline characteristics of the patients are presented in Table IA.

Older age, gastrointestinal bleeding (GIB), persistent duration, elevated WBC, platelet, and D-dimer in children with IgA vasculitis renal damage were statistically significant ($p < 0.05$). Multivariate stepwise binary logistic regression showed that, GIB, D-dimer, and age were independent risk factors for renal damage of IgA vasculitis (Table IB).

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Table IA: Baseline clinical data of the two groups.

Item	Non-renal injury (n = 49)	Renal injury (n = 68)	p-value
Boys	34 (57.6%)	25 (42.4%)	0.913 ^a
Age (years)	7.6 ± 2.63	9.45 ± 2.96	0.001 ^b
Abdominal pain	23 (57.5%)	17 (42.5%)	0.922 ^a
Arthralgia	27 (64.3%)	15 (35.7%)	0.312 ^a
GIB	9 (31.0%)	20 (69.0%)	0.001 ^a
URTI	36 (57.1%)	27 (42.9%)	0.817 ^a
ESR >20mm/h	10 (52.6%)	9 (47.4%)	0.596 ^a
CRP >5mg/L	27 (54%)	23 (36%)	0.435 ^a
Persistent purpura	16 (40%)	24 (60%)	0.004 ^a
IgG	11.06 ± 2.75	11.16 ± 2.77	0.844 ^b
IgA	1.97 ± 0.76	2.37 ± 0.85	0.009 ^b
IgM	1.41 ± 0.52	1.25 ± 0.44	0.071 ^b
D-dimer (mg/L)	0.71 (0.36 - 1.69)	2.21 (0.82 - 4.39)	<0.001 ^c
WBCs (10 ⁹ g/L)	9.14 ± 3.11	11.56 ± 5.7	0.004 ^b
Alb (g/L)	45.12 ± 5.48	44.04 ± 4.72	0.27 ^b
PT (s)	11.3 ± 0.81	11.23 ± 0.85	0.696 ^b
APTT (s)	28.77 ± 3.46	27.58 ± 2.87	0.052 ^b
PLT (10 ⁹ g/L)	312.75 ± 89.1	360.92 ± 95.08	0.006 ^b
BMI (kg/m ²)	16.63 (15.22 - 19.24)	16.67 (15.36 - 20.97)	0.41 ^c
Cr (umol/L)	34.57 ± 9.12	37.18 ± 9.7	0.14 ^b
BUN (mmol/L)	4.05 ± 1.16	3.79 ± 1.07	0.222 ^b

^aChi-square test; ^bt-test; ^cMann-Whitney U test.

Table IB: Univariate and multivariate logistic regression analyses of the risk factors of renal injury in patients with IgA Vasculitis.

Item	Univariate analysis		Multivariate analysis	
	(OR, 95% CI)	p-value	(OR, 95% CI)	p-value
D-dimer (mg/L)	1.323 (1.104 - 1.586)	0.002	1.259 (1.02 - 1.555)	0.032
PT (s)	0.913 (0.582 - 1.433)	0.693		
APTT (s)	0.889 (0.788 - 1.003)	0.056		
CRP	0.436 (0.64 - 2.821)	0.436		
ESR	1.305 (0.487 - 3.5)	0.597		
Respiratory infection	1.091 (0.522 - 2.28)	0.817		
Abdominal pain	1.039 (0.48 - 2.253)	0.922		
Arthralgia	0.67 (0.308 - 1.458)	0.313		
PLT (10 ⁹ g/L)	1.006 (1.001 - 1.010)	0.008	1.003 (0.98 - 1.009)	0.28
IgA	1.871 (1.147 - 3.054)	0.012	1.222 (0.684 - 2.184)	0.499
IgM	0.477 (0.211 - 1.079)	0.076		
IgG	1.014 (0.886 - 1.159)	0.842		
BMI (kg/m ²)	1.052 (0.962 - 1.150)	0.269		
GIB	4.521 (1.832 - 11.160)	0.001	3.262 (1.136 - 9.367)	0.028
Persistent purpura	3.12 (1.413 - 6.89)	0.005	1.793 (0.691 - 4.649)	0.23
Age (years)	1.271 (1.099 - 1.469)	0.001	1.223 (1.023 - 1.463)	0.027
Alb (g/L)	0.960 (0.890 - 1.034)	0.282		
WBCs (10 ⁹ g/L)	1.152 (1.037 - 1.280)	0.008	1.075 (0.937 - 1.234)	0.302
Boys	1.042 (0.5 - 2.172)	0.913	0.898 (0.353 - 2.287)	0.822

The optimal cut-off values for predicting renal injury were D-dimer level of 1.62 mg/L and age of 8.5 years. Figure 1A shows the age distribution with and without kidney injury. Figure 1B shows that elevated D-dimer levels significantly increase the risk of kidney injury in IgA vasculitis. Figure 1C shows that those patients with GIB were more likely to have renal injury.

Age, abdominal pain, GIB, persistent purpura, and recurrence have been considered as independent risk factors for renal injury.³ Renal involvement in IgA vasculitis has been reported to be more frequent in older children.⁴ Consistent with this observation, the authors found that the age of onset has a linear trend with the occurrence of nephritis, that is, the probability of occurrence increases by 1.223 times with the increase in age by one year. This study

showed that age of onset greater than 8.5 years was an independent risk factor for nephritis. Therefore, more attention should be paid to children with IgA vasculitis onset of age 8.5 or older.

Severe abdominal pain and GIB made IgA vasculitis patients more prone to kidney damage⁵ were confirmed in this study. GIB was an independent risk factor for renal injury by multivariate regression analysis: Patients with GIB were 3.26 times more likely to develop nephritis than patients without GIB, suggesting that gastrointestinal symptoms may be indicators of extensive, active IgA vasculitis.

Few reports are available on the value of D-dimer in forecasting renal injury with IgA vasculitis. Sun *et al.*⁶ reported that D-dimer combined with three metabolic biomarkers

improved the prediction accuracy of Henoch-Schonlein Purpura Nephritis (HSPN). In the present study, the authors identified that elevated D-dimer upon admission was an independent predictor of the outcome of patients with IgA vasculitis. Thus, D-dimer can be utilised as a useful biomarker of HSP severity and prognosis, and it can aid in the clinical management of this disease.

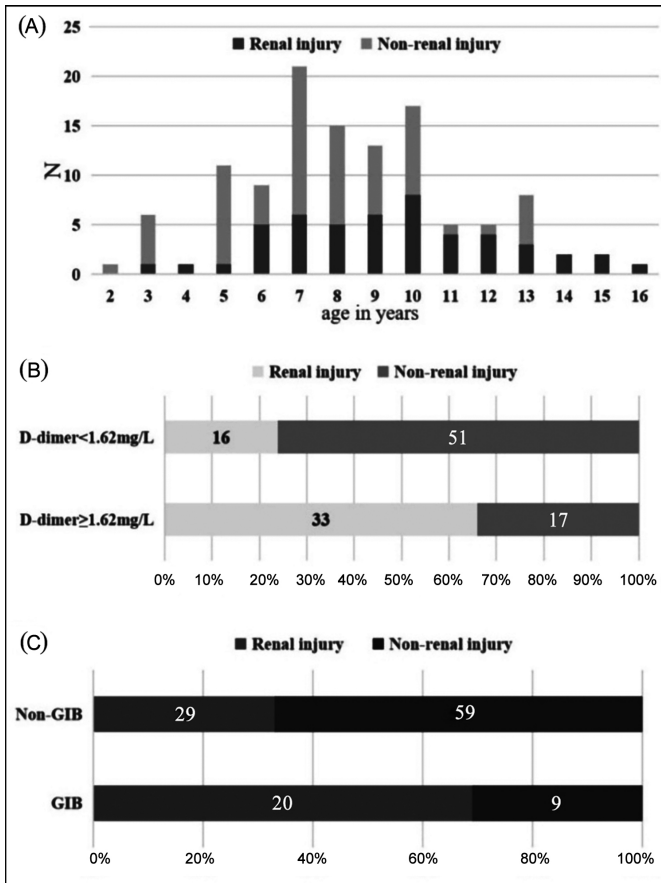


Figure 1: Predictive model for the occurrence of renal injury in patients with IgA Vasculitis. (A) Age distribution and occurrence of renal injury in 117 children with IgA Vasculitis. (B) Comparison of renal injury by D-dimer at a 1.62 mg/L cut-off point. (C) Predictive model for the occurrence of renal injury in patients with (GIB).

Elevated D-dimer levels indicate hypercoagulability in children with HSP, which may be related to the following factors. First, the damaged vascular endothelial cells initiate coagulation pathways and amount of coagulation substances are released, causing fibrinogen to be deposited on the damaged vascular wall. The avascular necrosis caused by these processes further activates the coagulation and fibrinolytic systems, leaving the body in a hypercoagulable state. Second, most of the children had been exposed to infection before IgA vasculitis; the inflammatory factors secreted by the accumulated white blood cells and neutrophils can cause damage to vascular endothelium and aggravate the above coagulation processes. Finally, children in the acute phase of IgA vasculitis have limited movement, which may slow blood flow and increases the risk of thrombosis.

This study found that higher levels of D-dimer significantly increased the probability of kidney injury in IGA vasculitis. This study also provides a theoretical basis for future anticoagulation therapy. Multi-centred and studies with larger sample size are needed to confirm this study's conclusions in the future.

Elevated D-dimer level, older age, and GIB were potential risk factors for renal damage in children with IgA vasculitis. Patients with these risk factors should be actively treated and closely followed up.

ETHICAL APPROVAL:

The study was approved by the ethics committee of the Affiliated Hospital of Xuzhou Medical University, Jiangsu, China.

PATIENTS' CONSENT:

Informed consent was obtained from the parents of the patients.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SM: Contributed to the conception and design of the study, acquisition of data, and drafting of the manuscript.
 XC: Assisted in data collection and analysis and critically revised the manuscript for important intellectual content.
 DW: Participated in the design of the study and performed the statistical analysis.
 XL: Involved in drafting of the manuscript and revised it critically for important intellectual content.
 GJ: Conceived and designed the analysis, collected the data, and contributed to the writing of the manuscript.
 All authors approved the final version of the manuscript to be published.

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