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Original Article

The predictive value of recurrent respiratory tract infection and serum ASO, D-D, IgA, β2-MG for renal injury in children with Henoch-Schonlein purpura

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Abstract: Objective: To investigate the predictive value of recurrent respiratory tract infection (RRTI) and serum antistreptolysin O (ASO), D-dimer (D-D), immunoglobulin A (IgA) and β2-microglobulin (β2-MG) in renal injury in children with Henoch-Schonlein purpura (HSP). Methods: Clinical data of 252 children with HSP were retrospectively analyzed. Patients were divided into renal injury and non-renal injury groups based on whether renal injury occurred. RRTI incidence and serum levels of ASO, D-D, IgA and β2-MG were compared between the groups. Multivariate logistic regression was used to screen independent predictors. Internal validation was performed using Bootstrap resampling (1,000 iterations). Receiver operating characteristic (ROC) curve and decision curve analysis (DCA) were applied to evaluate model performance and clinical net benefit. Results: The incidence of RRTI and levels of serum ASO, D-D, IgA and β2-MG in the renal injury group were significantly higher than those in the non-renal injury group ($P < 0.05$). Multivariate Logistic regression analysis identified RRTI and elevated ASO, D-D, IgA, and β2-MG as independent predictors ($P < 0.05$). The combined model achieved an AUC of 0.772, with an optimism-corrected AUC of 0.745 after bootstrap validation, significantly outperforming each single indicator. DCA confirmed that the combined model had the highest clinical net benefit within the risk threshold range of 0.1-0.9. Conclusions: The five-indicator combined model demonstrates preliminary predictive potential as an early screening tool of HSP renal injury. However, further multi-center external validation is required to confirm its generalizability before routine clinical application.

Keywords: Henoch-Schonlein purpura, kidney injury, recurrent respiratory tract infection, antistreptolysin O, d-dimer, immunoglobulin A, β2-microglobulin, predictive value

Introduction

Henoch-Schönlein purpura (HSP), also known as IgA vasculitis (IgAV), is a systemic vasculitis mediated by immune complexes, characterized by IgA deposition in the wall of small blood vessels. Its clinical manifestations are diverse, including not only palpable skin purpura, abdominal pain, and arthralgia [1], but also renal involvement such as hematuria and proteinuria [2]. Kidney injury is an important factor affecting the prognosis of the disease [3]. About 20-80% of children with HSP may have renal injury in 1-2 months after onset. In severe cases, it may even progress to end-stage renal failure [4] and seriously affects the physical and mental health of children [5].

Anti-streptolysin O (ASO) is an antibody produced in the body after streptococcal infection. Streptococcal infection is closely related to the occurrence of HSP and may be an important factor in inducing HSP and HSP nephritis (HSPN) [6]. D-dimer (D-D) is a marker of the activation of the fibrinolytic system. Abnormally elevated levels of D-D often indicate the risk of hypercoagulability and thrombosis in the body [7]. The increase of D-D is an independent predictor of gastrointestinal involvement in HSP [8]. Immunoglobulin A (IgA) is a key molecule mediating the immune response of HSP. Its serum levels not only reflect the immune status but are also closely correlated with the pathogenesis and prognosis of HSP [9]. β2-microglobulin (β2-MG) is mainly produced by lymphocytes. It can

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be freely filtered through the glomerulus and is almost completely reabsorbed in the proximal renal tubules. It is a sensitive marker reflecting glomerular filtration and renal tubular reabsorption. The serum level increases significantly when kidney injury occurs. It is widely used for early screening and condition assessment of kidney disease [10, 11].

At present, systematic studies on RRTI and the above four serum indicators combined to predict HSP renal injury are still limited. The purpose of this study was to comprehensively evaluate the predictive value of RRTI and serum ASO, D-D, IgA, as well as β2-MG for renal injury in children with HSP, construct a clinically applicable risk prediction formula, and provide evidence-based basis for clinical construction of an economical and convenient risk assessment system.

Materials and methods

Research object

This retrospective study included children with HSP who presented to the Department of Pediatrics at Linquan County People's Hospital (Fuyang, Anhui Province) between January 2021 and September 2024. A total of 252 HSP children were included and divided into a renal injury group (n = 72; HSPN group) and non-renal injury group (n = 180; non-HSPN group) according to the occurrence of renal injury during the disease course. This study was approved by the Hospital Ethics Committee of Linquan County People's Hospital (Approval number: SL-YJ2026-25). Informed consent was waived due to the retrospective study design.

Inclusion criteria: (1) Met the diagnostic criteria for HSP [12]; (2) Age ≤ 14 years; (3) First onset; (4) Complete clinical data. Exclusion criteria: (1) Combined with primary kidney disease, systemic lupus erythematosus or other connective tissue disease; (2) Received glucocorticoid or immunosuppressive therapy before admission; (3) Combined with severe infectious diseases, liver dysfunction or malignant tumor; (4) Incomplete clinical data. Exclusion of urinary tract infection and other causes of urinary abnormalities and in line with any of the following can be diagnosed as renal injury: (1) Hematuria: gross hematuria or three times within a week red blood cells ≥ 3 in high power field under the microscope (using morning urine after centrifugation); (2) Proteinuria: 3 consecutive non-same-day urine routine protein qualitative positive (morning urine sample); 24 h urinary protein > 150 mg or urinary protein/Cr > 0.2; urine microalbumin was higher than normal value for three consecutive times [13].

Data collection

General clinical data: including age, sex, weight, course of disease at admission, joint symptoms, RRTI and gastrointestinal symptoms. Laboratory indicators: serum ASO, plasma D-D, serum IgA, fibrinogen (Fib), white blood cell count (WBC), platelet count (PLT), neutrophil/lymphocyte ratio (NLR), β2-MG levels.

Detection methods

Venous blood samples (5 mL) were collected from all children on an empty stomach in the morning of the next day after admission to the EDTA anticoagulant tube. After centrifugation at 3000 r/min for 15 minutes (r = 13.5 cm), the supernatant serum was aspirated by a sterile pipette and stored in an EP tube. Cryopreservation was performed at -80°C. The levels of serum ASO, IgA and β2-MG were detected by immunoturbidimetry, and the level of serum D-D was detected by latex enhanced immunoturbidimetry. All tests were performed in strict accordance with the kit instructions and the kits were purchased from Shanghai Kehua Bioengineering Co., Ltd.

Statistical analysis

SPSS 27.0 software was used for data analysis. Shapiro-Wilk test was used to evaluate the normality of continuous data. The data of normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent sample t test was used for comparison between groups. Non-normal distribution data were expressed as median (interquartile range) [M (P25, P75)]. Mann-Whitney U test was used for comparison between groups. The categorical data were expressed as frequency (percentage) [n (%)]. Chi-square (χ^2) test or Fisher's test was used for comparison between groups. Univariate and multivariate Logistic regression analyses were used to analyze the risk factors of renal injury in children with HSP. The receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was calculated to evaluate the predictive efficacy of each index

alone and in combination for HSP renal injury. De-Long was used to test the difference between AUCs. To quantify the risk of overfitting and assess acceptable internal stability, we performed a Bootstrap internal validation with 1,000 resamples using the bias-corrected and accelerated (BCa) method. The Hosmer-Lemeshow goodness-of-fit test was performed to evaluate the calibration of the multivariate logistic regression model. A non-significant $P > 0.05$ was considered indicative of acceptable model fit. Decision curve analysis (DCA) was performed to calculate the net benefit of each prediction model under different risk thresholds, and evaluate the clinical practical value of the model. Two side $P < 0.05$ was considered statistically significant.

Results

Comparison of general clinical data between the two groups

Among the 252 children with HSP, 143 (56.7%) were male and 109 (43.3%) were female, with an average age of 9.05 ± 2.46 years. There were 72 cases (28.6%) with renal injury (HSPN group) and 180 cases (71.4%) without (non-HSP group). There were no significant differences in age, sex composition, weight and course of disease at admission between the two groups ($P > 0.05$). The incidence of RRTI in HSP group was 58.3% (42/72), which was significantly higher than 42.2% (76/180) in non-HSP group ($\chi^2 = 5.361$, $P = 0.021$). There was no significant difference in the proportion of joint symptoms and gastrointestinal symptoms between the two groups ($P > 0.05$) (**Table 1**).

Comparison of hematological indexes between the two groups

The median serum ASO level in HSPN group was 399.20 (179.55, 488.73) IU/mL, which was significantly higher than 299.95 (246.48, 348.73) IU/mL in non-HSPN group ($Z = 2.873$, $P = 0.004$). The plasma D-D level in HSPN group was 1.91 ± 0.52 mg/L, which was significantly higher than 1.63 ± 0.49 mg/L in non-HSPN group ($t = 4.012$, $P < 0.001$). The serum IgA level in HSPN group was 1.85 ± 0.62 g/L, which was significantly higher than 1.53 ± 0.41 g/L in non-HSPN group ($t = 4.742$, $P < 0.001$). The serum β2-MG level in HSPN group was 1.99 ± 0.46 mg/L, which was significantly higher than 1.71 ± 0.52 mg/L in non-HSPN group ($t = 3.841$, $P < 0.001$). See **Table 2** for details.

Correlation analysis between hematological indexes

Correlation analysis was performed in all 252 children. The results showed that there was a positive correlation between ASO, D-D, IgA, and β2-MG. Specifically, the correlation between D-D and β2-MG was the strongest ($r = 0.46$, $P < 0.001$) and the correlation between ASO and D-D was the weakest ($r = 0.22$, $P < 0.001$) (**Figure 1**).

Univariate logistic regression analysis of renal injury in HSP

Univariate logistic regression analysis was performed on baseline and laboratory indicators (such as age, gender, RRTI, ASO, D-D, IgA, β2-MG, etc.) with renal injury as the dependent variable. The results showed that RRTI (OR = 1.92, 95% *CI* 1.10-3.33, $P = 0.021$), elevated levels of ASO (OR = 1.01, 95% *CI* 1.01-1.01, $P < 0.001$), IgA (OR = 3.72, 95% *CI* 2.052-6.76, $P < 0.001$), D-D (OR = 3.07, 95% *CI* 1.71-5.50, $P < 0.001$) and β 2-MG (OR = 2.95, 95% *CI* 1.64-5.31, $P < 0.001$) were independent predictors of renal injury in children with HSP (**Table 3**). The variance inflation factor (VIF) values for RRTI, ASO, IgA, D-D, and β2-MG were 1.013, 1.135, 1.154, 1.310, and 1.324, respectively.

Multivariate logistic regression analysis of renal injury in HSP

With the occurrence of renal injury as the dependent variable, the variables with statistically significant differences in univariate analysis ($P < 0.1$) were included in multivariate logistic regression analysis. The results showed that RRTI (OR = 2.14, 95% *CI* 1.2216-3.76, $P = 0.008$), elevated ASO (OR = 1.00, 95% *CI* 1.00-1.02, $P = 0.035$), elevated IgA (OR = 2.70, 95% *CI* 1.44-5.09, $P = 0.002$), elevated D-D (OR = 1.56, 95% *CI* 1.06-2.30, $P = 0.024$) and elevated β2-MG (OR = 2.60, 95% *CI* 1.37-4.95, $P = 0.003$) were independent predictors of renal injury in children with HSP. Among them, IgA had the highest predictive strength (OR = 2.70), followed by β2-MG (OR = 2.60) (**Table 4**).

Prediction model formula construction

Based on the results of multivariate logistic regression analysis, a quantitative risk prediction formula for renal injury in children with HSP was constructed, which can be used for clinical rapid assessment of renal injury risk in children

Table 1. Comparison of baseline characteristics between the two groups

Variables	Non-HSPN group (n = 180)	HSPN group (n = 72)	t/χ^2	*P*
Sex [Male, n (%)]	104 (57.8)	39 (54.2)	0.273	0.601
Age (years)	9.32 ± 2.74	8.92 ± 2.34	1.160	0.247
Weight (kg)	31.35 ± 3.748	30.93 ± 4.22	0.789	0.431
The course of admission (days)	7.85 ± 3.47	8.46 ± 3.24	1.282	0.201
Joint symptoms [n (%)]	124 (68.9)	43 (59.7)	1.933	0.164
RRTI [n (%)]	76 (42.2)	42 (58.3)	5.361	0.021
Digestive tract symptoms [n (%)]	92 (51.1)	40 (55.6)	0.407	0.523

RRTI: recurrent respiratory tract infection.

Table 2. Comparison of hematological parameters between the two groups

Variables	Non-HSPN group (n = 180)	HSPN group (n = 72)	t/Z	*P*
ASO (IU/mL)	299.95 (246.48, 348.73)	399.20 (179.55, 488.73)	2.873	0.004
IgA (g/L)	1.53 ± 0.41	1.85 ± 0.62	4.742	< 0.001
D-D (mg/L)	1.63 ± 0.49	1.91 ± 0.52	4.012	< 0.001
Fib (g/L)	3.48 ± 0.76	3.33 ± 0.92	1.417	0.158
WBC ($\times 10^9$/L)	10.66 ± 4.52	11.73 ± 5.01	1.644	0.101
PLT ($\times 10^9$/L)	357.13 ± 74.33	373.25 ± 79.75	1.523	0.129
NLR	2.95 (1.70, 4.00)	2.70 (1.73, 3.88)	0.022	0.982
β2-MG (mg/L)	1.71 ± 0.52	1.99 ± 0.46	3.841	< 0.001

ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; Fib: fibrinogen; WBC: white blood cell count; PLT: platelet count; NLR: neutrophil/lymphocyte ratio.

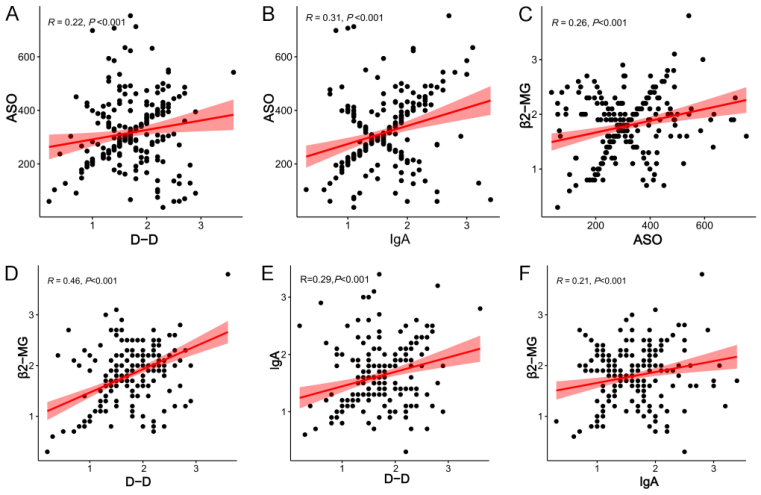


Figure 1. Correlation analysis between hematological indexes. A. Scatter plot of correlation coefficient between ASO and D-D. B. Scatter plot of correlation coefficient between ASO and IgA. C. Scatter plot of correlation coefficient between ASO and β2-MG. D. Scatter plot of correlation coefficient between D-D and β2-MG. E. Scatter plot of correlation coefficient between D-D and IgA. F. Scatter plot of correlation coefficient between IgA and β2-MG. ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin.

with HSP. The logit transformation formula of the prediction model is as follows: logit(P) = -6.31 + 0.76 × RRTI + 0.01 × ASO + 0.99 × IgA + 0.44 × D-D + 0.96 × β2-MG. The probability of renal injury is calculated as: P = 1/(1 + EXP (-logit (P))). For example, a child with HSP with the following clinical indicators: with recurrent respiratory tract infection, ASO = 400 IU/mL, IgA = 1.8 g/L, D-D = 2.0 mg/L, and β2-MG = 1.9 mg/L. The calculation process is as follows: logit(P) = -6.31 + 0.76 × 1 + 0.01 × 400 + 0.99 × 1.8 + 0.44 × 2.0 + 0.96 × 1.9 = 0.895. P = 1/(1 + EXP (-0.895)) ≈ 0.710. That is, the risk of renal injury in this child is 71.0%, which belongs to the high-risk group of renal injury, and clinical monitoring and early intervention should be strengthened. The Hosmer-Lemeshow goodness-of-fit test yielded a chi-square value of χ^2 = 13.280 (df = 8, *P* = 0.103), indicating good calibration of the logistic model, with no significant discrepancy between predicted and observed outcomes.

Table 3. Univariate logistic regression analysis of factors associated with renal injury in HSP

Variables	β	S.E	Z	*P*	OR (95% *CI*)
Sex					
Male					1.00 (Reference)
Female	0.15	0.28	0.52	0.601	1.16 (0.67-2.01)
Joint symptoms					
No					1.00 (Reference)
Yes	-0.40	0.29	-1.39	0.166	0.67 (0.38-1.18)
RRTI					
No					1.00 (Reference)
Yes	0.65	0.28	2.3	0.021	1.92 (1.10-3.33)
Digestive tract symptoms					
No					1.00 (Reference)
Yes	0.29	0.28	1.04	0.300	1.34 (0.77-2.33)
Age	0.07	0.06	1.16	0.247	1.07 (0.96-1.20)
Birth weight	-0.03	0.04	-0.79	0.430	0.97 (0.91-1.04)
The course of admission	0.05	0.04	1.28	0.201	1.05 (0.97-1.14)
ASO	0.01	0.00	3.36	< .001	1.01 (1.01-1.01)
IgA	1.31	0.30	4.31	< .001	3.72 (2.05-6.76)
D-D	1.12	0.30	3.77	< .001	3.07 (1.71-5.50)
Fib	-0.25	0.18	-1.41	0.158	0.78 (0.55-1.10)
WBC	0.05	0.03	1.63	0.102	1.05 (0.99-1.12)
PLT	0.00	0.00	1.52	0.130	1.00 (1.00-1.01)
NLR	0.00	0.10	0.02	0.981	1.00 (0.83-1.21)
β2-Mg	1.08	0.30	3.61	< .001	2.95 (1.64-5.31)

ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; RRTI: recurrent respiratory tract infection; Fib: fibrinogen; WBC: white blood cell count; PLT: platelet count; NLR: neutrophil/lymphocyte ratio.

Table 4. Multivariate logistic regression analysis of renal injury in HSP

Variables	β	S.E	Z	*P*	OR (95% CI)
Intercept	-6.31	0.99	-6.40	< .001	0.00 (0.00-0.01)
RRTI					
No					1.00 (Reference)
Yes	0.76	0.29	2.65	0.008	2.14 (1.22-3.76)
ASO	0.01	0.005	2.11	0.035	1.01 (1.00-1.02)
IgA	0.99	0.32	3.09	0.002	2.70 (1.44-5.09)
D-D	0.44	0.20	2.26	0.024	1.56 (1.06-2.30)
β2-Mg	0.96	0.32	2.97	0.003	2.60 (1.37-4.95)

ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; RRTI: recurrent respiratory tract infection.

ROC curve analysis of single indicator for predicting renal injury

ROC curve analysis was performed on variables with $P < 0.05$ in the multivariate analysis. The results showed that the AUC for RRTI was 0.581 (95% *CI* 0.503-0.659), with a sensitivity of 58.3% and a specificity of 57.8%. The AUC of ASO was 0.616 (95% *CI* 0.517-0.714). With the cutoff value of 394.1 IU/mL, the sensitivity was 54.2% and the specificity was 91.0%. The AUC for IgA was 0.656 (95% CI 0.574-0.737). With the cutoff value of 1.75 mg/L, the sensitivity was 58.3% and the specificity was 69.4%. The AUC of D-D was 0.658 (95% *CI* 0.581-0.735). With the cutoff value of 2.15 g/L, the sensitivity was 40.3% and the specificity was 85.6%. The AUC for β2-MG was 0.664 (95% CI 0.591-0.736). With the cutoff value of 1.85 mg/L, the sensitivity was 72.2% and the specificity was 61.3%. The ROC curves for each indicator are shown in **Figure 2**. Comparison of the AUC values among these indicators revealed no statistically significant difference ($P > 0.05$) (**Table 5**).

ROC curve analysis of combined indicators to predict renal injury

The AUC value of the combined model of the five indicators was 0.772 (95% *CI* 0.713-0.832). The sensitivity was 80.6% and the specificity was 63.9% (**Figure 3**). The De-Long test showed that the AUC value of the combined model was significantly higher than that of the single index ($P < 0.05$) (**Table 6**). To assess the potential overfitting of the combined prediction model, we performed an internal validation using the bootstrap method with 1,000 resamples. The optimism-corrected AUC of the five-indicator combined model was 0.745 (original apparent AUC = 0.772), with an optimism of 0.027. This suggests that the model exhibited acceptable internal stability without severe overfitting.

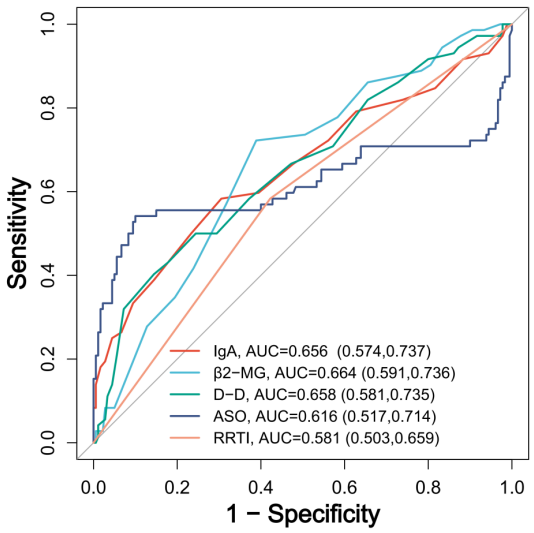


Figure 2. ROC curve analysis of single indicator for predicting renal injury. The sensitivities of IgA, β2-MG, D-D, ASO and RRTI were 58.3%, 72.2%, 40.3%, 54.2% and 58.3%, respectively. The specificities were 69.4%, 61.3%, 85.6%, 91.0% and 57.8%, respectively. The optimal cut-off values were 1.75 mg/L, 1.85 mg/L, 2.15 g/L, 394.1 IU/mL, respectively. Since RRTI is a binary variable, it has no optimal cut-off value. ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; RRTI: recurrent respiratory tract infection.

Decision curve analysis

To further verify the clinical practical value of the prediction model, DCA was performed on RRTI, ASO, IgA, D-D, β2-MG single indicators and the five-index combined model. The net benefit of each model under different renal injury risk thresholds (0-1) was calculated, and the clinical applicability of the model was evaluated by comparing the net benefit. The results showed that within the risk threshold range of 0.1-0.9 (the clinically common decision threshold range for HSP renal injury), the five-index combined prediction model had the highest clinical net benefit, which was significantly better than that of all single indicators. When the risk threshold was 0.2-0.6, the net benefit advantage of the combined model was the most significant, which could provide the most accurate clinical decision support for clinicians (**Figure 4**).

Discussion

In this study, we systematically analyzed the clinical and laboratory data of 252 children with HSP and identified RRTI and elevated ASO, D-D, IgA, β2-2-MG as independent predictors of renal injury in children with HSP. Among them, elevated IgA had the highest predictive strength (OR = 2.70). There was no significant difference in the AUC values of the single indicator. The prediction efficiency of the combined prediction model (AUC = 0.772) was significantly better than that of each single indicator.

This study showed that the incidence of RRTI in HSPN group (58.3%) was significantly higher than that in non-HSPN group (42.2%). Multivariate analysis confirmed that RRTI was an independent predictor of HSP renal injury (OR = 2.14). A large sample study of 517 children with HSP showed that respiratory tract infection within 2 weeks before admission was an independent risk factor for HSPN (OR = 1.744, 95% *CI* 1.003-3.031) [14]. This result provides strong clinical evidence for the infection-driven theory. Upper respiratory tract infection has been found to be a possible cause of HSP progression to nephritis [15]. From the perspective of pathophysiological mechanism, pathogens may directly damage the respiratory mucosal barrier, thereby increasing antigen exposure and immune activation. Infection-induced release of proinflammatory cytokines can increase glomerular capillary permeability and promote immune complex deposition [16]. And it can promote the deposition of IgA and other immune complexes in the mesangial area of the kidney, activate the local inflammatory response of the kidney, and further aggravate the renal tissue damage [17]. Therefore, for children with HSP and RRTI, it is necessary to strengthen the monitoring of renal injury-related indicators and be alert to the occurrence of renal injury.

The study has shown that elevated ASO is an independent predictor of renal injury in HSP (OR = 1.00). As a specific marker of streptococcal infection, the increase of ASO level suggests that there is a recent streptococcal infection or immune response after infection in children [18]. Study has shown that streptococcal infection is a common cause of HSP infection [19]. Pan et al. found that ASO ranked first among the 11 most important features for predicting renal injury in 217 children with IgA Vasculitis (IgAV) through machine learning methods [20]. It further confirms the important role of streptococcal infection in HSP renal injury.

Table 5. De-Long test of the AUCs between single indicators

Test pair	Z	*P*	AUC difference	95% *CI*
RRTI vs ASO	-0.571	0.568	-0.035	-0.157, 0.086
RRTI vs IgA	-1.386	0.166	-0.075	-0.181, 0.031
RRTI vs D-D	-1.421	0.155	-0.078	-0.184, 0.029
RRTI vs β2-MG	-1.532	0.126	-0.083	-0.189, 0.023
ASO vs IgA	-0.640	0.522	-0.040	-0.161, 0.082
ASO vs D-D	-0.608	0.543	-0.042	-0.178, 0.094
ASO vs β2-MG	-0.749	0.454	-0.048	-0.172, 0.077
IgA vs D-D	-0.045	0.964	-0.003	-0.114, 0.109
IgA vs β2-MG	-0.140	0.889	-0.008	-0.120, 0.104
D-D vs β2-MG	-0.111	0.912	-0.005	-0.102, 0.091

ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; RRTI: recurrent respiratory tract infection.

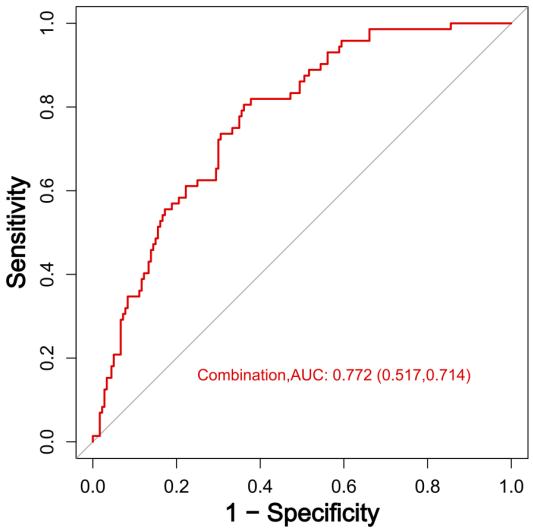


Figure 3. ROC curve analysis of combined indicators to predict renal injury. The sensitivity was 80.6% and the specificity was 63.9%.

This study showed that elevated D-D was an independent predictor of HSP renal injury (OR = 1.56). Min et al.'s retrospective cohort study of 117 children with IgA vasculitis showed that elevated D-D was an independent risk factor for renal injury [16]. The mechanism may be closely related to the pathological process of HSP. Abnormal glycosylation of IgA1 (Gd-IgA1) can lead to the formation of immune complexes, which are deposited on the wall of small blood vessels throughout the body and induce aseptic inflammation of small blood vessels [21]. The vasculitis further damages the endothelial structure, exposes subendothelial collagen and activates the coagulation pathway [22]. At the same time, microthrombus produced by platelet activation triggers compensatory fibrinolysis, and plasmin degrades cross-linked fibrin, producing D-D fragments, which eventually leads to increased D-D levels [23].

The core role of elevated serum IgA in the pathogenesis of HSP has been widely recognized. There are two subtypes of IgA, IgA1 and IgA2, with galactose-deficient IgA1 (Gd-IgA1) being the pathogenic form [24]. HSP is essentially a systemic vasculitis mediated by Gd-IgA1 immune complex deposition [25]. Yu et al. found that the AUC of plasma soluble CD89-IgA complex (sCD89-IgA) in predicting renal involvement was as high as 0.926 (sensitivity 94%, specificity 88%) [26]. sCD89-IgA is a potential biomarker for the development of renal involvement in children. However, it is difficult to fully reflect the true load of pathogenic IgA only by serum total IgA level. The study by Williams et al. have shown that novel biomarkers such as Gd-IgA1, IgA-containing circulating immune complexes (such as sCD89-IgA), urinary angiotensinogen and various complement proteins have shown great potential for early identification of IgAV [27]. Future research can consider integrating these new markers to further improve the predictive performance.

β2-MG is a small molecule globulin produced by cells in the body. It can pass freely through the glomeruli and is almost completely absorbed by the proximal tubules [28]. The increase of serum β2-MG can sensitively reflect the decrease of glomerular filtration rate or renal tubular reabsorption dysfunction. There was the strongest positive correlation between D-D and β2-MG (r = 0.454, $P < 0.001$) in our study, suggesting that glomerular microthrombosis was closely related to renal tubular injury in pathophysiology. In view of the highest AUC, simple detection and low cost of β2-MG, it is recommended to be used as an early screening index for renal tubular injury.

The AUC of combined detection of RRTI, ASO, D-D, IgA and β2-MG in predicting HSP renal injury was 0.772 (95% CI: 0.713-0.832, $P < 0.001$). And the sensitivity and specificity were

Table 6. De-Long test of the AUCs between combination and single indicators

Test pair	Z	*P*	AUC difference	95% *CI*
RRTI vs Combination	-4.901	< 0.001	-0.192	-0.269, -0.115
ASO vs Combination	-3.358	0.001	-0.157	-0.248, -0.065
IgA vs Combination	-3.441	0.001	-0.117	-0.184, -0.050
β2-MG vs Combination	-2.822	0.005	-0.109	-0.185, -0.033
D-D vs Combination	-2.445	0.014	-0.114	-0.206, -0.023

ASO: antistreptolysin O; D-D: D-dimer; IgA: immunoglobulin A; β2-MG: β2-microglobulin; RRTI: recurrent respiratory tract infection.

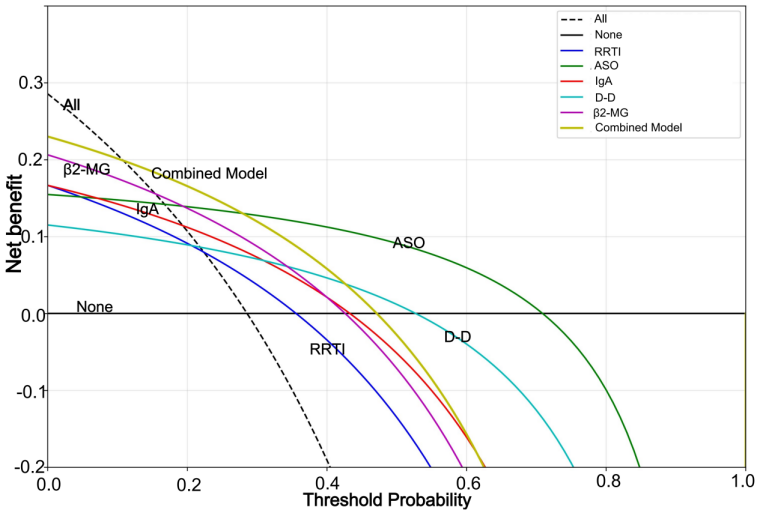


Figure 4. Decision curves of each prediction model for HSP renal injury. The horizontal axis represents the risk threshold of renal injury, and the vertical axis represents the clinical net benefit of the model. The higher the net benefit, the stronger the clinical practical value of the model. The five-index combined model has the highest net benefit in the clinically common threshold range of 0.1-0.9.

80.6% and 63.9%. It reflects the pathological state of children with HSP from multiple dimensions: RRTI reflects the background of infection triggering in children; ASO and IgA reflect the immune disorder of the body and the mechanism of renal injury mediated by immune complexes; D-D reflects the abnormal coagulation function and renal microcirculation disorder of the body; β2-MG directly reflects the parenchymal damage of the kidney. Each index reveals the mechanism of HSP renal injury from different angles. Combined detection can achieve complementary advantages and comprehensively evaluate the risk of renal injury in children. Compared with a single index, it can provide a comprehensive and reliable reference for clinical practice.

In this study, we further constructed a quantitative risk prediction formula based on multivariate logistic regression analysis, which can be directly used for clinical rapid calculation of the renal injury risk of children with HSP. The formula is simple to operate, only needs to input the routine clinical indicators of children, and can quickly obtain the risk probability of renal injury, which is suitable for popularization and application in primary hospitals, and provides a convenient and economical risk assessment tool for clinical early screening of high-risk children with HSP renal injury. In addition, the DCA results confirmed that the combined model had the highest clinical net benefit within the clinically common risk threshold range of 0.1-0.9, which could effectively avoid unnecessary invasive examinations and overtreatment for low-risk children, and timely implement intensive monitoring and intervention for high-risk children, further verifying the clinical application value of the model.

This study has some limitations. This study is a single-center retrospective study conducted exclusively at a county-level hospital in northern Anhui, China. The cohort predominantly represents the rural, resource-limited population of this specific region, which may differ significantly from children treated at tertiary referral centers or in other geographic areas. The sample size is relatively limited and there may be selection bias. Our findings require validation in a multi-center, large-sample prospective study. The judgment of RRTI depends on the review of medical history and there may be a recall bias. In the future, objective etiological test data can be used to supplement it. The optimal cut-off values of some indicators have not been unified and there are differences between different studies. More specific markers such as Gd-IgA1 and renal histopathology were not included and the model efficiency still had room for improvement. In addition, we did not perform a

direct head-to-head comparison between our combined model and previously published HSP renal injury risk scoring systems. Such a comparison is challenging due to differences in predictor sets, outcome definitions (biopsy-proven nephritis vs. early renal injury vs. severe kidney disease), and model presentation formats across studies. Although our model demonstrated acceptable internal stability, the lack of external validation in an independent multicenter cohort remains a major limitation. The model's generalizability to other populations requires further confirmation.

Conclusion

RRTI and serum ASO, D-D, IgA, β2-MG are independent risk factors for renal injury in children with HSP. The five-indicator combined prediction model shows preliminary utility for early identification of high-risk children. However, due to the lack of external validation, this model should be applied with caution in clinical practice. Future multi-center prospective studies are essential to externally validate and calibrate the model before it can be recommended for routine widespread use.

Disclosure of conflict of interest

None.

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