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Original Article

Development and validation of a nomogram to predict recurrence in children with Henoch-Schönlein purpura

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Abstract: Background: To screen risk factors for the recurrence in children with Henoch-Schönlein Purpura (HSP) and to develop and validate a nomogram for recurrence in children with HSP. Methods: During September 2019 and September 2021, 212 children with HSP were selected in this study. The children were divided into two sets in a proportion of 7:3 using R language, with the first group as the training sets and the second as the internal validation sets. The related variables were analyzed by univariate and multivariate logistic regression analyses, and a nomogram for predicting the recurrence in HSP children was established. The nomogram was evaluated by ROC curve, calibration curve and decision curve, and 1000 times bootstrap resampling method was used to verify the model internally. Results: Univariate and multivariate regression analyses identified respiratory infection, without preventive medication and diet restriction, age, allergen positive and abnormal urine routine as risk factors for the recurrence in children with HSP. Those risk factors were used to construct a predictive nomogram. The calibration curves revealed excellent accuracy of the predictive nomogram model, internally and externally. Conclusions: We constructed and validated a clinical nomogram to predict the recurrence in children with HSP. We confirmed that respiratory tract infection, without preventive medication and diet restriction, age, allergen positive and abnormal urine routine were independent recurrence risk factors. This nomogram had a good performance in clinical decision-making.

Keywords: Henoch-Schönlein purpura, nomogram, risk predictors, recurrence

Introduction

Henoch-Schönlein Purpura (HSP) is one of the most common vasculitis in children [1]. About 90% HSP patients are less than 10 years old, with an average of 6 years old [2, 3]. Sensitizing factors may enter the body, produce immune response, and deposit on the small blood vessels, resulting in aseptic vasculitis and purpura [4-6]. The clinical manifestations include non-thrombocytopenic purpura of skin and mucosa, gastrointestinal bleeding, joint swelling and pain, renal damage, myocarditis, liver damage and intracranial hemorrhage [7]. The recurrence rate is high, which is up to 30%~40% within 1 year [8, 9]. Frequent recurrence may develop into chronic disease and increase the risk of renal damage [10-13].

At present, there is no consensus on the recurrence rate of HSP. Some studies have shown that frequent recurrence will lead to the chronic progress of children's condition, which will affect children's health and quality of life [14-17]. At the same time, some studies believed that recurrent rash, glucocorticoid use, older age, respiratory tract infection after initial cure are the risk factors of HSP recurrence [18-22].

This study aimed to screen risk predictors of recurrence in children with HHSP and develop and validate a nomogram for recurrence in children with HSP.

Materials and methods

Study design

This retrospective study was performed at Cangzhou Central Hospital from September 2019 and September 2021. Inclusion criteria: 1) Children with an age at <18 years old; 2) Children with HSP that diagnosed in line with the new classification standard of vasculitis

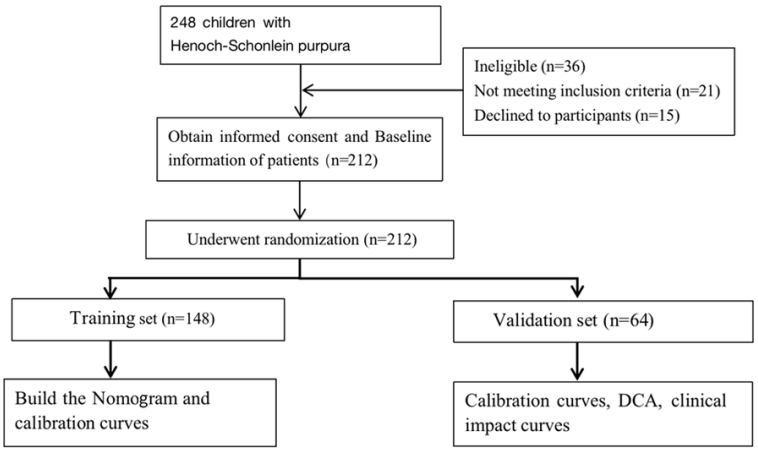

Figure 1. Flow chart showing recruitment.

and in children formulated by the European Alliance against Rheumatism and the European Society of Paediatric Rheumatology in 2006 [23]; and 3) Children with first-time diagnosis of recurrent HSP (reappearance of symptoms of HSP after disappearing for 2 weeks to 3 months or more). Exclusion criteria: 1) Children who didn't meet the clinical diagnostic criteria of HSP; 2) Children with severe dysfunction of other organs or other types of skin diseases; 3) Children with congenital immunodeficiency; 4) Children who were lost during regular follow-up. This study was approved and recognized by the Ethics Committee of Cangzhou Central Hospital (ECZZX-2019.0212).

Data collection and measurement

We collected the demographic and clinical data, such as gender, allergen results, family history, leukocyte count, eosinophil count and platelet count, of all children who met the inclusion criteria. After discharge, outpatient follow-up was conducted to record the recurrence, preventive drug administration, respiratory tract infection, diet control, exercise restriction, etc.

Development and validation of the nomogram model

The primary cohort of HSP children were divided into two sets in a proportion of 7:3 using R language, with the first group as the training set and the second as the internal validation set. Based on the data set, the univariate and multivariate regression analysis were used to select the optimal risk factors for the recurrence prediction in children with recurrence HSP. Then, according to the multivariate logistic regression results, the nomogram was constructed to visually score the individual risk probabilities of children with recurrence HSP. The receiver operating characteristic (ROC) curve was used to test the discriminant efficiency of the model. To determine the clinical usefulness of the model, decision curve analysis was used to quantify the benefit of the nomogram under different thresholds in the set.

Statistical analysis

SPSS 20.0 software was used to analyze the data. The measurement data were expressed by X±s or median. Independent sample t-test or rank sum test was used for inter-group comparison; The counting data were expressed in percentage (%), and X^2 test was used for comparison. The analysis of risk factors was processed by binary logistic regression analysis. $P<0.05$ showed that the difference was statistically significant. The independent risk factors obtained from the results of univariate and multivariate logistic regression analysis were diagnosed by multicollinearity. R software establishes nomogram and ROC curve of prediction model; ROC curve is described by the area under the curve; The calibration ease of the model is evaluated by the calibration ease of the software. Decision curve (DCA) analysis was used to estimate the clinical practicability of the new nomogram Finally, the model is internally verified by using 1000 resampling methods, and the AUC after resampling is calculated.

Result

Participant recruitment

Figure 1 showed the recruitment of participants in this study. We recruited 212 participants were eligibility for this study, according to the statistical results, the children with recurrence HSP were 89 cases, and 123 children were without recurrence. Then, the 212 children were divided into training set and valida-

Table 1. Comparison of clinical data between the three groups

Indexes	recurrence group (*n*=89)	non-recurrence group (*n*=123)	*P value*
Age (years)	4.6±1.3	8.6±2.1	0.004
Gender			0.726
Male (n%)	56 (62.9%)	87 (70.7%)	
Female (n%)	33 (37.1%)	36 (29.3%)	
Respiratory infection			0.005
Yes	77 (86.5%)	43 (35%)	
No	12 (13.5%)	80 (65%)	
Preventive medication			0.011
Yes	18 (20.2%)	88 (71.5%)	
No	71 (79.8%)	35 (28.5%)	
Diet restriction			0.001
Yes	39 (43.8%)	84 (68.3%)	
No	50 (56.2%)	39 (31.7%)	
Allergen			0.042
Positive	77 (86.5%)	54 (43.9%)	
Negative	12 (13.4%)	69 (56.1%)	
Urine routine			0.0001
normal	5 (5.6%)	90 (73.2%)	
abnormal	84 (94.4%)	33 (26.8%)	
Hormone drugs			0.092
Had	75 (84.3%)	111 (90.2%)	
No	14 (15.7%)	12 (9.8%)	
the time of therapy begin	4.01±2.20	4.5±1.8	0.318

Note: P<0.05.

tion set according to the ratio of 7:3 using R language.

Clinical characteristics

Table 1 shown characteristics of the participants. The research included 212 patients after follow-up with 89 patients in recurrence HSP (recurrence group) and 123 patients in non-recurrence HSP (non-recurrence group). The results showed that there were significant differences in the factors like age, respiratory infection, preventive medication, diet restriction, allergen, and urine routine between two groups (all P<0.05); however, there were no statistical differences in gender, taking hormone drugs and the time to start therapy between two groups (P>0.05).

Characteristics of training set and validation set

Table 2 shows the characteristics of training set and validation set, the results demonstrated that there were statistical differences in age, respiratory infection, preventive medication, diet restriction, allergen, and urine routine between the training set and validation set (all P<0.05).

Univariate and multivariate regression analysis

As shown in **Table 3**, Kaplan Meier method was used for univariate analysis. The results showed that age, gender, respiratory infection, preventive medication, diet restriction, allergen, and urine routine were correlated with the recurrence of HSP, and the difference was statistically significant (all P<0.05). Taking hormone drugs and the time of therapy had no correlation with the recurrence of HSP (P>0.05). The significant single factors (age, gender, respiratory infection, preventive medication, diet restriction, allergen, and urine routine) were analyzed by Cox proportional hazards regression model. The results showed that respiratory infection, no preventive medication, no diet restriction, age, allergen positive and abnormal

Table 2. Characteristics of the training and validation sets

	Training set (n=148)			Validation set (n=64)		
	Recurrence (n=56)	Non recurrence (n=92)	P	Recurrence (n=33)	Non recurrence (n=31)	P
Age	3.10±2.05	5.87±3.06	0.03	2.99±1.90	4.2±1.91	0.005
Gender			0.01			0.005
Female	20 (35.7%)	20 (21.7%)		2 (9.1%)	1 (10%)	
Male	36 (64.3%)	72 (78.3%)		20 (90.9%)	15 (90%)	
Respiratory infection			0.003			0.002
Yes	47 (83.9%)	32 (34.8%)		30 (90.9%)	11 (35.5%)	
No	9 (16.1%)	60 (65.2%)		3 (9.1%)	20 (64.5%)	
Preventive medication			0.001			0.02
Yes	12 (21.4%)	61 (66.3%)		6 (18.2%)	27 (87.1%)	
No	44 (78.6%)	31 (33.9%)		27 (81.8%)	4 (12.9%)	
Diet restriction			0.009			0.03
Yes	30 (53.6%)	76 (82.6%)		9(27.3%)	8 (25.8%)	
No	26 (46.4%)	16 (17.4%)		24(72.7%)	23 (74.2%)	
Allergen			0.008			0.01
Positive	50 (89.3%)	44 (47.8%)		27(81.8%)	10 (30.3%)	
Negative	6 (10.7%)	48 (52.2%)		6 (18.2%)	21 (69.7%)	
Urine routine			0.001			0.006
normal	4 (7.1%)	78 (84.8%)		1 (3%)	12 (38.7%)	
abnormal	52 (92.9%)	14 (15.2%)		32 (97%)	19 (61.3%)	
Hormone drugs			0.005			0.03
Had	49 (87.5%)	86 (93.5%)		26 (78.8%)	26 (80.6%)	
No	7 (12.5%)	6 (6.5%)		7 (21.2%)	6 (19.4%)	
the time of therapy begin (Days)	3.3±1.92	2.9±1.56	0.193	2.5±2.1	2.9±1.8	0.221

urine routine were independent risk factors of recurrence in HSP patients.

Development of nomogram model

Based on the results of the above multivariate Cox regression analysis, we constructed a 6-factor nomogram using the data of the training set and then calculated the nomogram score of each patient in the model. The graph showed that the corresponding score of nomogram was higher in children with age ≥4 years old and no preventive medication, while the corresponding score was lower in HSP children with allergen negative (**Figure 2**).

Validation of a nomogram model

The unadjusted concordance index (C-index) for the nomogram was 0.859 [95% confidence interval (CI), 0.815-0.994]. The calibration plot of the nomogram is shown in **Figure 3**. The AUC for the nomogram was 0.886179 (**Figure 4**). It indicated that the nomogram could accurately predict the recurrence in children with HSP.

The decision curve analysis (DCA)

Decision curve analysis (DCA) of the model is shown in **Figure 5**, and the DCA of model demonstrated that if the threshold probability of recurrence in children with HSP was 20 to 90%, the validity of the model to predict recurrence in children with HSP was increased. This predictive model was suitable for clinical use.

Discussion

As shown in the study, respiratory infection, without preventive medication and diet restriction, age over 4 years old, allergen positive and abnormal urine routine were independent predictors for recurrence in Children with HSP. Moreover, we developed a predictive nomogram model to predict the risk of recurrence in

Table 3. Univariate and Multivariate Risk analysis

Indexes	Univariate		Multivariate	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Age				
0-1	Reference		Reference	
1-3	0.58 [0.5989-0.973]	0.3306	1.180 (1.046-1.330)	0.007
≥4	1.11 [0.963-1.1532]	0.005	1.032 (1.010-1.056)	0.005
Gender				
Female	Reference		Reference	
Male	0.23 [0.133-0.636]	0.004	1.08 [0.77-1.38]	0.16
Respiratory infection				
Yes	Reference		Reference	
No	1.32 [0.9206-0.982]	0.001	1.42 [0.85-0.95]	0.028
Preventive medication				
Yes	Reference		Reference	
No	1.36 [0.414-0.892]	0.003	1.59 [1.12-2.26]	0.02
Diet restriction				
Yes	Reference		Reference	
No	1.42 [0.639-0.928]	0.004	1.15 [1.014-1.09]	0.04
Allergen	Reference		Reference	
Positive	1.25 [1.1615-1.189]	0.028	1.754 [1.241-2.479]	0.003
Negative	1.36 [0.414-0.892]	0.0086	2.36 [1.29-4.30]	0.006
Urine routine				
normal	Reference		Reference	
abnormal	1.95 [0.6390-0.6522]	0.022	1.58 [0.77-0.38]	0.016
Hormone drugs				
Had	Reference			
No	1.84 [0.69-1.014]	0.98		

these children. The calibration plot and AUC plot of the nomogram model showed that the clinical model had good accuracy and clinical applicability with a high C-index (0.859). The DCA demonstrated clinical usefulness of this nomogram for predicting recurrence in children with HSP. In addition, this model would enable early recognition of recurrence in HSP children.

The results of this study showed that respiratory infection after initial cure is a risk factor for the recurrence of HSP in children. Most children have a history of upper respiratory tract infection 1-3 weeks before the onset, and its pathogens include adenovirus and group A β hemolytic streptococcus, staphylococcus aureus, chlamydia pneumoniae, mycoplasma pneumoniae, hepatitis B virus, hepatitis C virus, and parvovirus B19, etc [24-27]. At present, the mechanism of HSP recurrence induced by infection is not completely clear. It is generally believed that susceptible individuals can produce a variety of inflammatory mediators after infection with pathogens, resulting in increased capillary permeability of the whole body. At the same time, the immune balance of the body is disturbed, B lymphocytes are activated, stimulating the production of a large number of immune complexes, which were dominated by IgA and deposited in the wall of small blood vessels of the whole body, and finally, HSP recurrence occurred [28, 29].

Preventive medication improves the imbalance of immune function and effectively prevents the recurrence of HSP. The results showed that without preventive medication after cure was a risk factor for HSP recurrence. The use of spleen Aminopeptide [30], pidotimod [31] and other drugs have been reported to be able to prevent the recurrence of HSP.

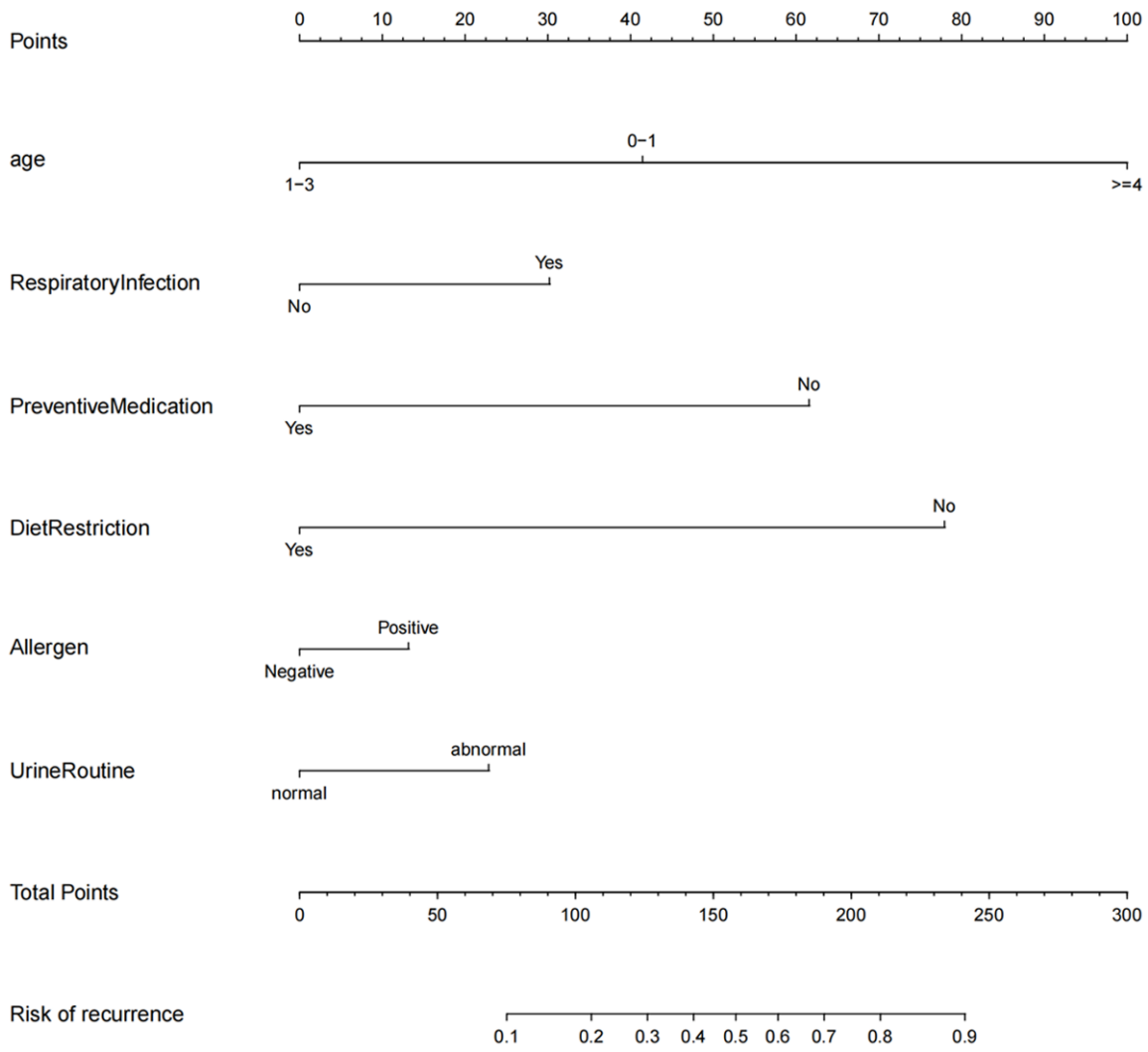

Figure 2. The nomogram for predicting recurrence in children with Henoch-Schönlein Purpura.

Diet control mainly refers to the restriction of food consumption and types. 90% of the allergens in food are protein. Fish, shrimp, milk and eggs are rich in heterologous protein. Eating such food or excessive intake in children with HSP or whose digestive function has not recovered is easy to stimulate the gastrointestinal tract in a high-sensitive state, resulting in HSP recurrence [32, 33]. Therefore, effective dietary control plays an important role in avoiding disease recurrence.

Inappropriate exercise after the initial cure is a risk factor for the recurrence of HSP. This may be related to the fact that strenuous exercise increases the chance of capillary injury, causes excessive fatigue and is easy to induce upper respiratory tract infection [34, 35]. At this time, the sudden increase of exercise accelerates the blood circulation, which may damage the capillaries in the repair stage again and increase the risk of HSP recurrence [36].

This study found that the recurrence of HSP is related to age. Those with older onset age are prone to HSP recurrence, which is consistent with the results of Karadağ Şerife Gül et al. [37]. It is speculated that the immune response of older children is stronger than that of younger children [38], or older children have more exposure opportunities and are more likely to be exposed to infectious sources and allergens.

The results also showed that some allergen are prone to cause HSP recurrence. There are many kinds of allergens, especially food allergens such as milk, fish, shrimp and crab [39, 40].

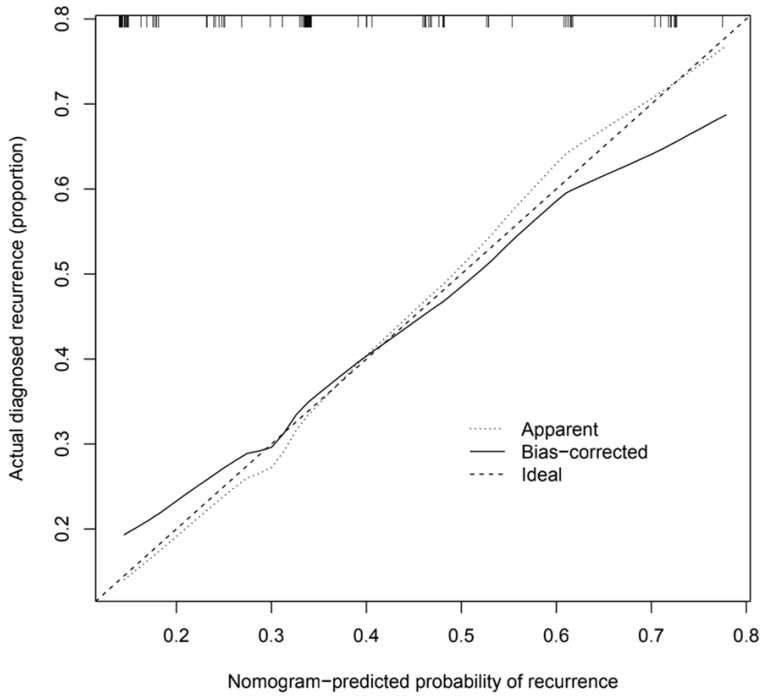

Figure 3. The calibration curves for predicting recurrence in children with Henoch-Schönlein Purpura.

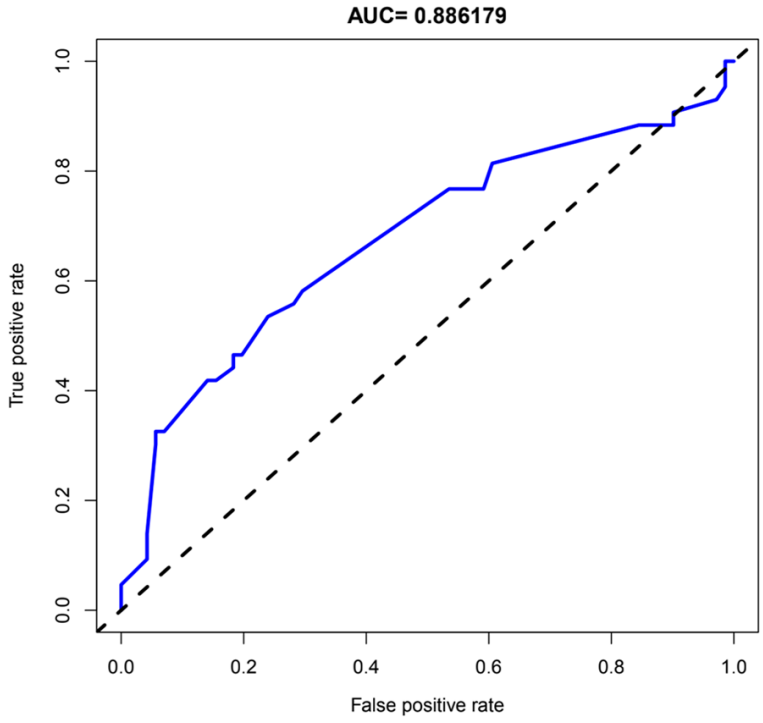

Figure 4. ROC curves for predicting recurrence in children with Henoch-Schönlein Purpura nomogram.

The reason is that after entering the digestive tract, food will be converted into energy, amino acids, glycerol and monosaccharides by digestive tract, but many foods cannot be fully digested by the body due to the lack of corresponding enzymes. Those undigested substances enter the intestine in the form of polypeptide or other molecules and are recognized as foreign substances, which cause immune reaction, produce food specific IgG antibody, form immune complex after binding with food molecules, thus induce type III allergy [41], and then cause HSP recurrence.

Renal damage is a serious complication of HSP. According to statistics, 20%~50% of children with HSP can have renal involvement, mostly 4-6 weeks after the onset [42, 43]. The results of this study show that the first onset with renal damage is a risk factor for the recurrence of HSP. Studies have shown that positive proteinuria is a risk factor for HSP recurrence as well [44, 45]. Binet et al. [46] reported that the occurrence of hematuria is significantly correlated with HSP recurrence. Therefore, in the early stage of renal damage in children with HSP, attention should be paid to timely treatment and intervention to avoid disease recurrence.

There are some limitations in our study. Firstly, our study was a retrospective study. We could not avoid the influence of selection bias since the study only included HSP patients with recurrence. Secondly, this research was a single center and small sample study. A larger, multi-center study is needed to verify its applicability.

In summary, this study constructed a predictive nomogram model with good accuracy and clinical applicability. This may help to early predict

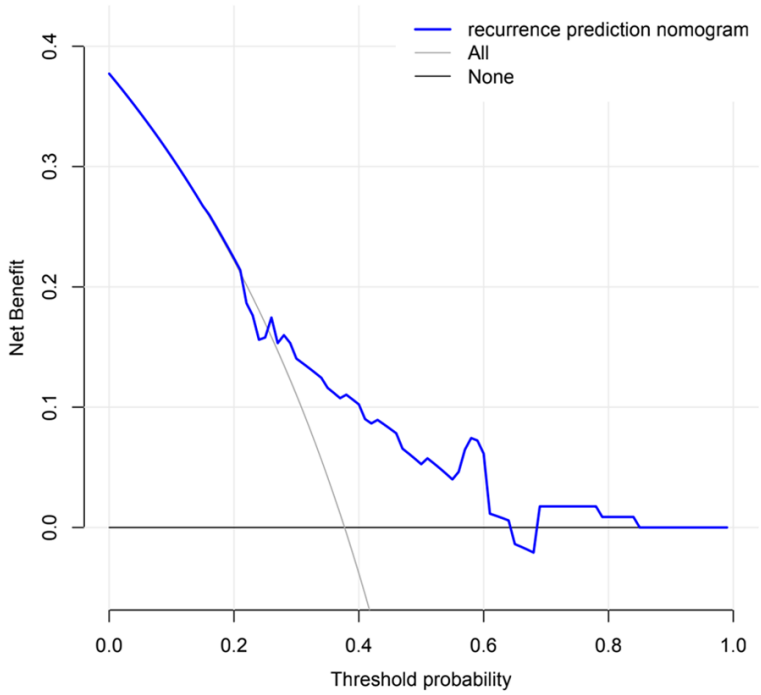

Figure 5. Decision curve analysis for the nomogram.

recurrence in children with HSP. In addition, the data supported that respiratory infection, without preventive medication and diet restriction, older age, positive allergen and abnormal urine routine are the independent risk factors.

Disclosure of conflict of interest

None.

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