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ORIGINAL ARTICLE

Correlations of Leukotriene B4 and 25-Hydroxyvitamin D3 Levels with Disease Severity in Children with Henoch-Schonlein Purpura

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SUMMARY

Background: **The aim was to explore the correlations of leukotriene B4 (LTB4) and 25-hydroxyvitamin D_3 [25(OH)D_3] levels with disease severity in children with Henoch-Schonlein purpura (HSP).**
Methods: **A total of 260 HSP children admitted from January 2017 to December 2018 were selected, and 60 healthy children physically examined in the same period were enrolled as controls. The results of general laboratory tests and expression levels of leukotriene B4 (LTB4) and 25-hydroxyvitamin D_3 [25(OH)D_3] were compared. The correlations of LTB4 and 25(OH)D_3 with immunoglobulin A (IgA) were statistically analyzed, and the expression levels of LTB4 and 25(OH)D_3 were compared between Henoch-Schonlein purpura nephritis (HSPN) group and non-Henoch-Schonlein purpura nephritis (NHSPN) group. The optimal cutoff values of LTB4 and 25(OH)D_3 to predict HSP were analyzed by receiver operating characteristic (ROC) curves, based on which they were divided into low-, intermediate-, and high-risk groups. The length of hospital stay and recurrence rate within 6 months were compared.**
Results: **The levels of white blood cell count, platelets, C-reactive protein, IgA, IgM, IgE, complement C3, and LTB4 were significantly higher and 25(OH)D_3 was lower in HSP group than those in control group ($p < 0.05$). IgA, LTB4, and 25(OH)D_3 levels were independent risk factors for HSP ($p < 0.05$). LTB4 was positively correlated with IgA ($p < 0.05$), and 25(OH)D_3 was negatively correlated with IgA ($p < 0.05$). LTB4 level was significantly higher and 25(OH)D_3 level was lower in HSPN group than those in NHSPN group ($p < 0.05$). The optimal cutoff values of LTB4 and 25(OH)D_3 were 27.82 pg/mL and 22.10 ng/mL, respectively, the length of hospital stay gradually increased in low-, intermediate-, and high-risk groups, and the recurrence rates within 6 months were 14.2%, 31.5%, and 39.6%, respectively ($p < 0.05$).**
Conclusions: **LTB4 level increases and 25(OH)D_3 level decreases in children with HSP, and the expression levels are significantly correlated with disease severity, suggesting predictive values for prognosis.**
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INTRODUCTION

Henoch-Schonlein purpura (HSP) is the most common autoimmune vasculitis syndrome in childhood. It is a systemic small-vessel vasculitis that is manifested as palpable cutaneous purpura, arthritis or arthralgia, nephritis, abdominal pain, and gastrointestinal bleeding in clinic [1]. The etiology and pathogenesis of HSP remain

unclear, but relapse often occurs, seriously affecting the health of children. In recent years, researchers have paid more attention to the effects of immune disorders in the pathogenesis, including humoral immune disorders, cellular immune imbalances, and the release of various inflammatory factors [2]. Leukotriene B4 (LTB4) is an important inflammatory mediator that participates in the pathological processes of inflammatory diseases such as asthma, allergic rhinitis, urticaria and inflammatory bowel disease, and a large amount of LTB4 is released at the late phase of allergic inflammation [3]. 25-hydroxyvitamin D_3 [25(OH)D_3] is most suitable to reflect vitamin D level in the human body, and it can regulate immune function and inflammatory response in multiple ways [4]. The decreased expression level of 25(OH)D_3 is highly associated with the onset of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, and its active metabolites are closely related to the occurrence and progression of the disease [5]. Given the significance of LTB4 and 25(OH)D_3 for immunity, inflammation, and allergy treatment, this study aimed to investigate the correlations of LTB4 and 25(OH)D_3 levels with severity of HSP, and to provide new ideas for exploring the etiology of HSP.

MATERIALS AND METHODS

Baseline clinical data

A total of 260 children diagnosed with HSP for the first time and admitted to our hospital from January 2017 to December 2018 were selected, including 155 males and 105 females with an average age of 6.58 ± 2.84 years old. According to the new criteria recommended by Expert Group of Chinese Medical Association in 2013 [6], the diagnostic criteria of HSP included (item 1 was a necessary condition, accompanied by at least one of 2 - 5): 1) palpable cutaneous purpura, 2) diffuse abdominal pain, 3) immunoglobulin A (IgA) deposits on biopsy of any areas of body, 4) arthritis or arthralgia, and 5) kidney involvement (hematuria and/or proteinuria). According to the presence or absence of kidney involvement, children with HSP were divided into Henoch-Schonlein purpura nephritis (HSPN) group (n = 27) and non-Henoch-Schonlein purpura nephritis (NHSPN) (n = 233). Besides, according to clinical manifestations, NHSPN group was categorized into 5 subgroups, namely simple group (simple cutaneous purpura, n = 37), gastrointestinal group (cutaneous purpura with gastrointestinal symptoms, n = 49), joint group (cutaneous purpura with joint symptoms, n = 77) and mixed group (cutaneous purpura with gastrointestinal and joint symptoms, n = 70).

Meanwhile, 60 healthy children physically examined in our hospital during the same period were enrolled as control group, including 38 males and 22 females with an average age of 7.03 ± 3.15 years old. No statistically significant difference was found in age and gender ratios between control group and case group.

Inclusion criteria: a) Patients aged 2 - 15 years old, and b) children's families who signed the informed consent, and the present study was approved by the Medical Ethics Committee of this hospital. Exclusion criteria: a) Patients who were administered with vitamin D or calcium within the past 3 months, b) those who received glucocorticoids or immunotherapy within the past 3 months, c) those with congenital cardiopulmonary diseases or cardiac insufficiency, or d) those with abnormal calcium or phosphorus metabolism, or chronic renal diseases.

Sample collection

About 2 mL of fasting venous blood was drawn from every research object in the early morning. After standing for 20 minutes, the samples were centrifuged at 2,000 rpm for 20 minutes. Subsequently, the supernatant was collected and stored in the refrigerator at -80°C. Enzyme-linked immunosorbent assay was utilized to detect serum LTB4 and 25(OH)D_3 levels [7,8].

Observation indices

Laboratory test indices of all research objects were collected, including routine blood tests (white blood cell count and platelets), blood biochemistry (triglycerides and total cholesterol), and immunological indices (C-reactive protein, IgG, IgA, IgM, IgE, C3, and C4).

Diagnostic criteria

1) HSPN met the diagnostic criteria formulated by Expert Group of Chinese Medical Association in 2013 [6]: hematuria and/or proteinuria within 6 months of the course of HSP.

2) HSP recurrence was considered as HSP children suffering typical manifestations again at least 1 month after the complete disappearance of clinical symptoms of HSP.

Follow-up

The presence or absence of skin rash, abdominal pain, arthritis and arthralgia as well as abnormal urine routines were followed up through telephone, outpatient reexamination and hospitalization within 6 months to determine the recurrence of HSP.

Statistical analysis

SPSS 19.0 software was employed for statistical analysis. The quantitative data conforming to normal distribution were expressed as mean ± standard deviation, *t*-test was used for comparison between groups, and analysis of variance was applied for comparison among multiple groups. If the data did not conform to normal distribution, they were expressed as median and interquartile range, and rank sum test was used for comparison between groups. The numerical data were expressed as percentage, and χ^2 test or Fisher's exact probability test was used for comparison between groups. Multivariate logistic regression analysis was utilized to explore the independent risk factors for HSP, and the correla-

Table 1. Laboratory test results.

Clinical symptom	HSP group (n = 260)	Control group (n = 60)	$\chi 2$	p
White blood cell count (10^9/L)	8.45 ± 2.21	6.62 ± 1.24	6.188	0.000
Platelets (10^9/L)	0.72 ± 0.17	0.57 ± 0.13	6.413	0.000
Triglycerides (mmol/L)	3.73 ± 1.21	3.44 ± 0.84	1.760	0.079
Total cholesterol (mmol/L)	35.30 ± 12.90	38.28 ± 14.01	1.587	0.114
C-reactive protein C (mg/L)	5.63 ± 2.84	4.41 ± 2.92	2.984	0.003
IgG (g/L)	8.92 ± 1.24	9.23 ± 1.76	1.601	0.110
IgA (g/L)	2.96 ± 0.86	1.67 ± 0.54	11.116	0.000
IgM (g/L)	1.51 ± 0.47	1.38 ± 0.32	2.035	0.043
IgE (IU/mL)	167.82 ± 106.30	132.63 ± 91.36	2.370	0.018
Complement C3 (g/L)	1.68 ± 0.37	1.21 ± 0.24	4.927	0.000
Complement C4 (g/L)	0.31 ± 0.05	0.32 ± 0.08	1.230	0.220
LTB4 (pg/mL)	75.25 ± 40.23	18.92 ± 4.31	10.819	0.000
25(OH)D3 (ng/mL)	20.12 ± 7.91	32.14 ± 9.70	10.146	0.000

$25(OH)D_3$ - 25-hydroxyvitamin D3, HSP - Henoch-Schonlein purpura, IgA - immunoglobulin A, IgE - immunoglobulin E, IgG - immunoglobulin G, IgM - immunoglobulin M, LTB4 - leukotriene B4.

Table 2. Multivariate logistic regression analysis results.

Variable	Regression coefficient (β)	SE	Wald	p	OR (95% CI)
IgA (g/L)	1.635	0.312	7.254	0.012	5.431 (2.635 - 6.432)
LTB4 (pg/mL)	1.543	0.258	5.378	0.023	3.104 (1.437 - 4.621)
25-(OH)D3 (ng/mL)	1.281	0.263	4.315	0.028	2.742 (1.052 - 3.186)

$25(OH)D_3$ - 25-hydroxyvitamin D3, IgA - immunoglobulin A, LTB4 - leukotriene B4, OR - odds ratio, SE - standard error.

tions were analyzed by Spearman's test. Besides, the predictive values of LTB4 and $25(OH)D_3$ for HSP were analyzed by receiver operating characteristic (ROC) curves. Two-tailed $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Laboratory test results

The levels of white blood cell count, platelets, C-reactive protein, IgA, IgM, IgE, complement C3, and LTB4 were significantly higher and $25(OH)D_3$ was significantly lower in HSP group than those in control group ($p < 0.05$) (Table 1).

Multivariate logistic regression analysis results

The factors with statistically significant differences between the above two groups of patients were included in the multivariate logistic regression analysis. The results indicated that IgA, LTB4, and $25(OH)D_3$ levels were independent risk factors for the occurrence of HSP ($p < 0.05$), and other factors failed to be incorporated into the logistic regression model (Table 2).

Correlations of LTB4 and $25(OH)D_3$ with IgA in children with HSP

LTB4 was significantly positively associated with IgA ($p < 0.05$), $25(OH)D_3$ was significantly negatively correlated with IgA ($p < 0.05$), and no prominent correlations were found between the two indices and IgE. The results showed that IgA may rise with the increased expression level of LTB4 and the decreased expression level of $25(OH)D_3$ (Table 3 and Figure 1).

LTB4 and $25(OH)D_3$ levels of different subgroups

LTB4 level was significantly higher and $25(OH)D_3$ level was significantly lower in HSPN group than those in NHSPN group ($p < 0.05$). Compared with simple group, LTB4 level was significantly higher in gastrointestinal

Table 3. Correlations of LTB4 and 25(OH)D$_3$ with IgA in children with HSP.

Group (g/L)	LTB4 (pg/mL)		25(OH)D3 (ng/mL)	
	r	p	r	p
IgA	0.658	0.000	-0.523	0.000
IgM	0.043	0.792	0.005	0.978
IgE	0.205	0.176	-0.021	0.625

25(OH)D$_3$ - 25-hydroxyvitamin D3, HSP - Henoch-Schonlein purpura, IgA - immunoglobulin A, IgE - immunoglobulin E, IgM - immunoglobulin M, LTB4 - leukotriene B4.

Table 4. LTB4 and 25(OH)D$_3$ levels of different subgroups.

Group	LTB4 (pg/mL)	$\chi 2$	p	25(OH)D3 (ng/mL)	$\chi 2$	p
NHSPN (n = 233)	72.32 ± 13.47			20.38 ± 5.48		
Simple (n = 37)	53.51 ± 12.46			22.51 ± 8.46		
Gastrointestinal (n = 49)	75.45 ± 36.21 #	3.527	0.001	19.45 ± 6.21	1.935	0.056
Joint (n = 77)	79.56 ± 45.17 #	3.438	0.001	20.56 ± 6.35	1.374	0.172
Mixed (n = 70)	72.71 ± 15.46 #	3.185	0.002	18.91 ± 3.46 #	3.111	0.002
HSPN (n = 27)	85.12 ± 16.23 *	4.571	0.000	18.02 ± 4.17 *	2.165	0.031

*** p < 0.05 vs. NHSPN group, # p < 0.05 vs. simple group. 25(OH)D$_3$ - 25-hydroxyvitamin D3, HSPN - Henoch-Schonlein purpura nephritis, LTB4 - leukotriene B4, NHSPN - non-Henoch-Schonlein purpura nephritis.**

Table 5. ROC curve analysis results of diagnostic values of LTB4 and 25(OH)D$_3$ for HSP.

Diagnostic index	AUC	Optimal cutoff	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
LTB4	0.792	27.82 (pg/mL)	62.43	81.50	74.35	88.46	65.20
25-(OH)D3	0.741	22.10 (ng/mL)	80.24	70.37	72.29	65.32	77.92

25(OH)D$_3$ - 25-hydroxyvitamin D3, AUC - area under the curve, HSP - Henoch-Schonlein purpura, LTB4 - leukotriene B4, ROC - receiver operating characteristic.

Table 6. Prognostic analysis of children with HSP in different risk stratifications.

Group	Length of hospital stay			Recurrence within 6 months		
	Day	t	p	n (%)	$\chi 2$	p
Low-risk (n = 120)	7.25 ± 1.50	7.408	0.000	17 (14.2)	15.043	0.000
Intermediate-risk (n = 92)	9.34 ± 2.25			29 (31.5)		
High-risk (n = 48)	13.50 ± 2.50			19 (39.6)		

HSP - Henoch-Schonlein purpura.

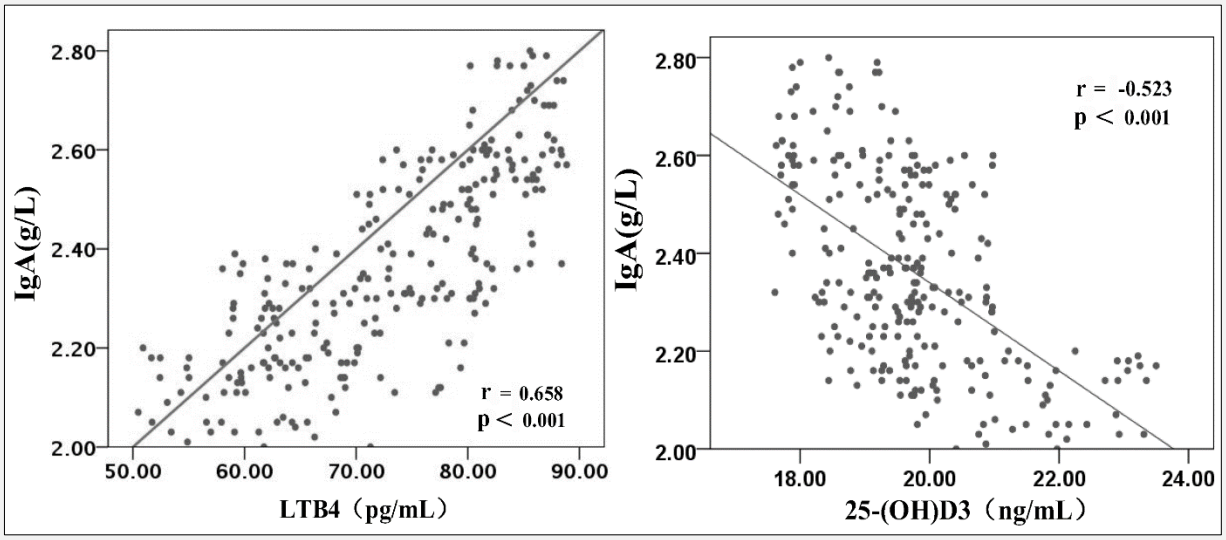

Figure 1. Correlations of LTB4 and 25(OH)D_3 with IgA in children with HSP.

25(OH)D_3 - 25-hydroxyvitamin D3, IgA - immunoglobulin A, LTB4 - leukotriene B4.

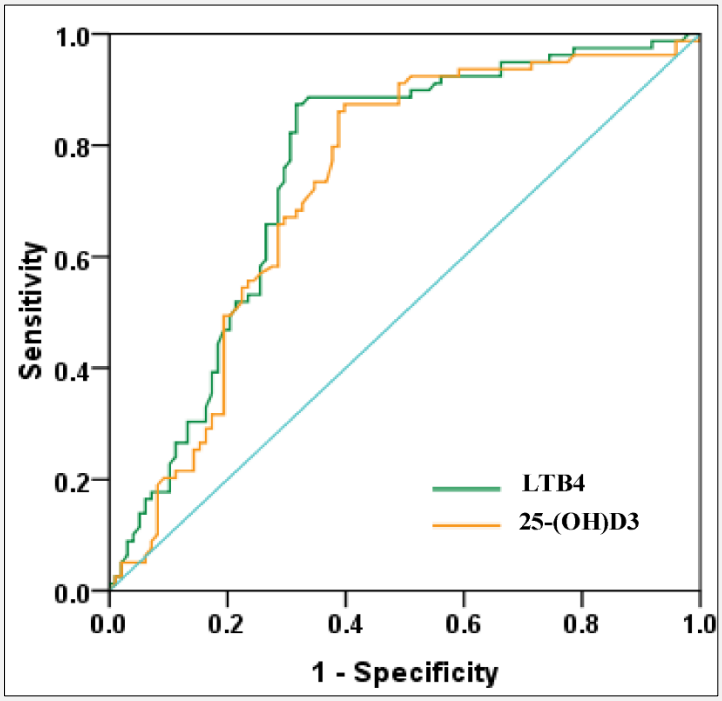

Figure 2. ROC curve analysis of diagnostic values of LTB4 and 25(OH)D_3 for HSP.

25(OH)D_3: 25-hydroxyvitamin D3; HSP: Henoch-Schonlein purpura; LTB4: leukotriene B4; ROC: receiver operating characteristic.

group, joint group, and mixed group than that in simple group, and 25(OH)D_3 level was significantly lower in mixed group ($p < 0.05$) (Table 4). The results demonstrated a higher expression level of LTB4 and a lower expression level of 25(OH)D_3 in the group with more serious conditions and complex symptoms.

ROC curve analysis results of diagnostic values of LTB4 and 25(OH)D_3 for HSP

The diagnostic value of LTB4 and 25(OH)D_3 in children with HSP was analyzed by ROC curve in this study. The results confirmed that the areas under the curve were 0.792 and 0.741 respectively, suggesting high diagnostic value, and the optimal cutoff values of LTB4 and 25(OH)D_3 were 27.82 pg/mL and 22.10 ng/mL, respectively (Table 5 and Figure 2).

Prognostic analysis of children with HSP in different risk stratifications

According to the optimal cutoff values of LTB4 and 25(OH)D_3, risk stratification was conducted in children with HSP, and they were categorized into low-risk group (LTB4 $\leq$ 27.82 pg/mL and 25(OH)D_3 > 22.10 ng/mL, n = 120), intermediate-risk group (LTB4 > 27.82 pg/mL or 25(OH)$D_3 \leq$ 22.10 ng/mL, n = 92), and high-risk group (LTB4 > 27.82 pg/mL and 25(OH)$D_3 \leq$ 22.10 ng/mL, n = 48). The length of hospital stay was longer in high-risk group, a total of 65 cases suffered recurrence manifested as skin rash, abdominal pain, and arthritis as well as abnormal urine routines within 6 months. Recurrence rates were 14.2%, 31.5%, and 39.6%, respectively, suggesting statistically significant differences ($p < 0.05$) (Table 6). The results indicated that the higher the risk-stratification based on LTB4 and 25(OH)D_3, the worse the prognosis.

DISCUSSION

The pathogenesis of HSP remains unclear. Previous studies have elucidated that HSP occurrence is dominated by the immune response that causes immune disorders, and also involves cellular immune markers, cytokines, and inflammatory transmitters. IgA-mediated immune response plays a crucial role in the pathogenesis. Due to increased activity of helper T lymphocytes and B lymphocytes, a large number of IgA immune complexes are produced and deposited in small vessel walls, causing capillary and small-vessel vasculitis, leading to blood extravasation to subcutaneous tissues and mucous membranes, resulting in abdominal pain, gastrointestinal bleeding and hematuria, according to different deposit sites [9]. Complement activation usually can be seen in the process of immune complex formation and deposition, namely increased level of complement C3 at the early phase and complement C4 deficiency in the capillary wall at the late phase, suggesting that C3 and C4 can serve as key molecules to activate alternative pathways [10]. The interaction between leukocytes and vascular endothelial cells is also involved in the pathogenesis of HSP. Endothelial injury, perivascular leukocyte infiltration, and chemokine and cytokine production play important roles in this process [11]. Besides, the elevated level of platelets that leads to abnormal coagulation also can be tested in HSP [12]. LTB4 is a powerful inducer and cell adhesion agent that has the function of chemotaxis of inflammatory cells to the site of inflammation. It serves as a key cytokine involved in body immunity and autoimmunity. LTB4 can participate in various diseases related to immunity and inflammation such as bronchiolitis, allergic rhinitis, dermatitis, and acute pulmonary injury [13]. Multiple immune cells such as macrophages, dendritic cells, T lymphocytes, and antigen-presenting cells can express 25(OH)D_3-1α hydroxylase and vitamin D receptors, thus regulating the normal function of cells, indicating vitamins D may play a role in inflammatory diseases [4]. Vitamin D is an important vitamin and a precursor of hormones in human body. Food-derived vitamins D2 and D3 and vitamin D3 synthesized by human body through the skin are inactive. After hydroxylation in the liver, lowly active 25 (OH)D_3 is produced and transported to the kidney to be further hydroxylated into highly active 1,25 (OH)D_3 which plays a regulatory role by binding its receptor. It is well-documented that vitamin D receptor is widely expressed in various tissues and immune cells. Vitamin D can regulate immune function, which has been closely correlated to allergic diseases [14-16]. 25(OH)D_3 is the main storage form of vitamin D in the human body, which is lowly expressed in the case of HSP [17]. In this study, it is also confirmed that LTB4 level was significantly higher and 25(OH)D_3 level was significantly lower in children with HSP than those in healthy control group.

Immunoglobulin, an important effector molecule involved in the body's specific humoral immune response, is a glycoprotein secreted by the proliferation and differentiation of B cells under the stimulation of foreign antigens, and it can be divided into five types, i.e. IgG, IgA, IgM, IgD, and IgE [18]. Among them, it is difficult to detect IgD due to the low level. Therefore, IgG, IgA, IgM, and IgE were detected in this study, and the results indicated that IgA, IgM and IgE levels in children with HSP were significantly increased, and no significant change was found in IgG expression. At present, there is no consensus with regard to the changes of IgG, IgM, and IgE in HSP serum in China and foreign countries, which needs further research with large sample size. Part of the results in this study is consistent with research by Purevdorj et al. [18]. The increase of IgA in children with HSP is consistent with previous studies [1,9,18], and the detection of serum IgA level offers an auxiliary means of diagnosing HSP. The correlations of LTB4 and 25(OH)D_3 with IgA, IgM, and IgE levels were further analyzed in this study, and the results demonstrated that LTB4 was significantly positively associated with IgA and 25(OH)D_3 was significantly negatively correlated with IgA, that is, the higher the IgA

level and the lower the 25(OH)D_3 level, the higher the IgA level, suggesting that LTB4 and 25(OH)D_3 are related to IgA in the occurrence of HSP.

Skin purpura, repeatedly occurring at the onset of HSP, is a necessary condition for the diagnosis of HSP. In addition, the digestive system, joints and kidneys are often involved, especially renal injury. Renal injury caused by HSP is called HSPN, which is of decisive significance to long-term prognosis [19]. Tan et al. reported that severe skin purpura was correlated with HSPN [20]. Jimenez et al. reported that a repeated onset of skin rash was associated with HSPN [21]. In this study, the expression levels of LTB4 and 25(OH)D_3 were compared between HSPN group and NHSPN group, and the results indicated that LTB4 level was significantly higher and 25(OH)D_3 level was significantly lower in HSPN group than those in NHSPN group. The LTB4 and 25(OH)D_3 levels of mixed group were higher and lower than those of simple skin purpura group, respectively, suggesting that LTB4 and 25(OH)D_3 can reflect the severity of HSP to a certain extent.

Generally, HSP has a good prognosis, but attacks may repeatedly occur in some cases, with varying interval from several weeks to months. In order to further explore the predictive value of serum LTB4 and 25(OH)D_3 expression levels for the prognosis of HSP, the optimal cutoff values of LTB4 and 25(OH)D_3 to predict the occurrence of HSP were analyzed by ROC curve were 27.82 pg/mL and 22.10 ng/mL, respectively. According to the optimal cutoff values, patients were categorized into low-, intermediate-, and high-risk groups, and the prognosis was compared among three groups of patients. The results indicated that high-risk group exhibited a longer length of hospital stay and a higher recurrence rate within 6 months, suggesting that the expression levels of LTB4 and 25(OH)D_3 can evaluate HSP children's prognosis to a certain extent.

CONCLUSION

In conclusion, LTB4 level is increased and 25(OH)D_3 level is decreased in children with HSP, and the expression levels are notably correlated with disease severity. Therefore, laboratory testing can be combined with the two indices to comprehensively evaluate the severity and prognosis of children with HSP, so as to provide more sufficient evidence for clinical diagnosis.

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Declaration of Interest:
The author declares no competing interest.

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