

Immunological Features of Children with Gastrointestinal Bleeding Due to Henoch-Schönlein Purpura

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Background: This study aims to evaluate the immunological features of gastrointestinal (GI) bleeding in children with Henoch-Schönlein purpura (HSP).

Study Design: This retrospective study was conducted on children with HSP. Demographic and clinical data were collected, including serum immunoglobulin (Ig) levels, complement C3 and C4 levels, and lymphocyte subtype percentage.

Results: A total of 446 hospitalized children had HSP. Eighty-six children with HSP had GI bleeding, 114 had proteinuria, and 107 had hematuria. Lower arthralgia, prolonged glucocorticoid use, increased white blood cell counts, elevated neutrophils and neutrophil-to-lymphocyte ratio, reduced IgG and C3 levels, elevated CD19⁺ cell percentage, and reduced CD3⁺ cell and natural killer cell percentages were associated with GI bleeding risk in patients with HSP. Multivariate regression analysis revealed that arthralgia, glucocorticoid use, increased neutrophil percentage, reduced IgG and C3 levels, and increased CD19⁺ cell percentage were independent predictors of GI bleeding. Further analysis indicated that the combination of C3 and CD19⁺ cell percentages had a high predictive ability for GI bleeding in children with HSP.

Conclusion: This study indicated that reduced C3 and increased CD19⁺ cell percentages contributed to the development of GI bleeding in children with HSP. Specific immunologic profiles may be strongly correlated with GI bleeding risk in children with HSP.

Keywords: children, complement, gastrointestinal bleeding, Henoch-Schönlein purpura, lymphocyte subtype

Introduction

Henoch-Schönlein purpura (HSP), also called IgA vasculitis (IgAV), is the most common form of systemic vasculitis in childhood. HSP is characterized by widespread leukocytoclastic vasculitis of small vessels resulting from vascular entrapment of circulating immunoglobulin A (IgA) immune complexes with complement activation.^{1,2} The reported incidence varied from 3 to 27 per 100,000 children, and the incidence could reach 56 per 100,000 Asian children with a peak incidence of five years.^{3,4} The clinical features of HSP include non-thrombocytopenic purpura, arthritis, arthralgia, gastrointestinal (GI) disorders, and renal involvement.¹ About two-thirds of children with HSP have abdominal pain with or without abdominal distension, nausea, vomiting, and GI bleeding.^{4,5} Although GI bleeding accounts for about 18–52% of HSP abdominal symptoms, it threatens children's lives.^{2,6,7} Furthermore, massive intestinal bleeding is associated with a significantly increased mortality.^{7,8} Some children with severe or refractory GI bleeding require long-term nutritional support and treatment.² This leads to substantially increased medical costs and longer hospital stays. Consequently, early detection of GI bleeding is crucial for HSP treatment and prognosis.

Clinical studies have shown that the platelet (PLT) counts, mean platelet volume (MPV), platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), C3 level, D-dimer level, and low-density lipoprotein level are associated with gastrointestinal hemorrhage in HSP.^{9–11} This is an important basis for doctors to diagnose the gastrointestinal bleeding status of HSP patients, which greatly aids clinical judgment. However, the etiology and pathogenesis of gastrointestinal

bleeding in patients with HSP remain unclear. Many studies have indicated that fluid and cellular immune dysfunctions contribute to HSP pathogenesis.^{12–14} Some studies have indicated that elevated blood NLR and decreased MPV can be good predictors of HSP in patients with symptoms of gastrointestinal involvement.^{15,16} Skin rash and elevated D-dimer levels may also cause GI bleeding. Considering the importance of the immune response in HSP, we hypothesized that immune function abnormalities may cause gastrointestinal bleeding in children with HSP.

Methods

Patients

This retrospective study was conducted on a primary cohort of patients with HSP between January 2017 and December 2022 at the Sichuan Maternal and Child Health Hospital (Sichuan, China). The patients were mostly aged 5–15 years. HSP diagnosis was based on the EULAR/PRINTO/PRES criteria, including purpura or petechiae with lower limb predominance and at least one of the following four criteria: abdominal pain, histopathology, arthritis or arthralgia, and renal involvement.¹⁷ Proteinuria was determined as >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample, and hematuria was determined as >5 red blood cells/high power field or red blood cells casts in the urinary sediment or $\geq 2+$ on the dipstick.¹⁷ GI bleeding included hematemesis, melena, and hematochezia. The HSP in children without GI bleeding were labeled as the control group. Patients with missing data were excluded from this study.

Detection of Lymphocyte Subtypes and Data Collections

Venous blood samples were collected within 24 h of admission. Lymphocyte subtype percentages were estimated using BD Multitest 6-color T, B, and NK (TBNK) lymphocytes Reagent via Cantoll (Becton Dickinson, San Jose, CA, USA) and analyzed using DIVA software (Becton Dickinson, San Jose, CA) according to the manufacturer's recommendations. Briefly, the CD3 FITC was used to identify T lymphocytes, CD4 PE-CyTM7 to detect T helper/inducer lymphocytes, CD8 APC-Cy7 to identify suppressor/cytotoxic T lymphocytes, and CD19 APC to identify B lymphocytes. The TBNK reagent defines NK cells by simultaneously analyzing the expression of CD16 and CD56 using the same conjugation.

Demographic and clinical data were collected, including age, sex, disease duration, complications, white blood cell (WBC) counts, neutrophil percentage, lymphocyte classification and counts, hemoglobin (Hgb) concentration, PLT counts, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), procalcitonin level (PCT), immunoglobulin (Ig)G, IgE, IgA, complement C3 and C4, CD19⁺, CD3⁺, CD4⁺, CD8⁺, and NK cell percentages. All laboratory tests were performed on admission.

Statistical Analysis

Continuous variables were expressed as mean and standard differences (SD) and compared using an unpaired, two-tailed *t*-test or Mann–Whitney test. Categorical variables were compared using the χ^2 test or Fisher's exact test. The logistic regression analysis was used to assess potential risk factors for developing GI due to HSP. The area under the receiver operating characteristic (ROC) curve was used to evaluate the predictive power of the logistic regression model. The PASW statistical software package was used to perform all statistical analyses and graphics. Moreover, $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by the Ethics Review Board of Sichuan Maternal and Child Health Hospital 20230331-030), which followed the ethical procedures established by the Declaration of Helsinki. Since the hospital ethics committee approved this retrospective study, all patients were anonymous, and independent informed consent was not required.

Results

Clinical Characteristics of HSP with GI Bleeding

Four hundred forty-six hospitalized children had HSP. In total, 86 children with HSP had GI bleeding, 114 had proteinuria, and 107 had hematuria (Table 1). The clinical characteristics of the HSP with GI bleeding and control

Table 1 Clinical Characteristics and Laboratory Findings Between Children with or Without GI Bleeding Due to IgAV

Variables	HSP with GI BLEEDING (n = 86)	HSP Without GI Bleeding (n = 360)	P-value
Gender (M/F)	49/37	203/157	0.510
Arthralgia (No/Yes)	63/23	189/171	< 0.001**
Proteinuria (No/Yes)	69/17	263/97	0.107
Hematuria (No/Yes)	67/19	272/88	0.380
WBC ($\times 10^9/L$)	13.86 \pm 5.96	11.73 \pm 5.30	0.001**
Neutrophil (%)	71.35 \pm 14.26	65.31 \pm 15.12	0.001**
Neutrophil/lymphocyte	3.66 \pm 3.27	2.67 \pm 2.25	0.009**
Hemoglobin (g/L)	128.26 \pm 13.15	127.37 \pm 11.74	0.540
Platelet ($\times 10^9/L$)	405.19 \pm 158.64	363.98 \pm 112.18	0.025*
CRP (mg/L)	10.51 \pm 17.79	7.60 \pm 13.48	0.160
ESR (mm/h)	8.15 \pm 7.18	15.78 \pm 15.55	< 0.001**
ALT (U/L)	13.93 \pm 9.85	13.56 \pm 11.29	0.785
AST (U/L)	28.68 \pm 22.26	31.82 \pm 19.97	0.212
LDH (U/L)	315.67 \pm 210.74	353.83 \pm 277.93	0.270
Creatine ($\mu g/L$)	45.20 \pm 13.37	36.77 \pm 11.29	< 0.001**
IgG (g/L)	9.40 \pm 3.58	10.80 \pm 3.36	0.003**
IgA (g/L)	1.99 \pm 0.68	2.08 \pm 0.81	0.329
IgE (U/L)	258.79 \pm 350.15	201.49 \pm 301.28	0.202
C3 g/L	1.17 \pm 0.24	1.26 \pm 0.24	0.010*
C4 g/L	0.33 \pm 0.12	0.36 \pm 0.15	0.185
CD19%	26.51 \pm 10.03	19.31 \pm 8.64	< 0.001**
CD3%	61.53 \pm 11.64	67.73 \pm 10.93	< 0.001**
CD4%	30.36 \pm 8.05	32.45 \pm 8.13	0.104
CD8%	24.88 \pm 7.79	26.95 \pm 7.14	0.067
NK cell%	7.09 \pm 4.49	9.66 \pm 6.53	0.009**

Notes: *P < 0.05, **P < 0.01.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, complement; CD, cluster of differentiation; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactic dehydrogenase; NK, natural killer; Hgb, hemoglobin; Ig, Immunoglobulin; PCT, procalcitonin; PLT, blood platelet; WBC, white blood cells.

groups are shown in Table 1. The HSP in children with GI bleeding had lower arthralgia frequency (26.7% vs 47.5%, $P < 0.001$), higher WBC counts (13.86 vs 11.73, $P = 0.001$), higher neutrophil percentage (71.35% vs 65.31%, $P = 0.001$), higher NLR (3.66 vs 2.67, $P = 0.009$), higher PLT counts (405.19 vs 363.98, $P = 0.025$), and higher serum creatine levels (45.2 vs 36.77, $P < 0.001$) compared to control group. There were no significant differences in gender ratio, proteinuria and hematuria quantities, Hgb concentrations, CRP levels, and liver function between the two groups.

Immunologic Features of GI Bleeding in Children with HSP

The HSP in children with GI bleeding showed higher CD19⁺ lymphocyte percentage (26.51% vs 19.31%, $P < 0.001$), lower CD3⁺ T cell (61.53% vs 67.73%, $P < 0.001$), lower NK cell percentage (7.09% vs 9.66%, $P = 0.009$), lower IgG levels (9.40% vs 10.80%, $P = 0.003$), and lower C3 levels (1.17 vs 1.26, $P = 0.01$) compared to those without GI bleeding (Table 1). However, patients with HSP who experienced GI bleeding had lower IgA and C4 levels and lower CD4⁺ and CD8⁺ cell percentages than those without GI bleeding. There was no statistically significant difference between the two groups.

Risk Factors for Developing GI Bleeding in HSP

Univariate logistic regression models used to predict GI bleeding in children with HSP depicted significant differences in most of the risk factors (Table 2). The clinical features most strongly associated with gastrointestinal bleeding were less

Table 2 Risk Factors Associated with the Development of GI Bleeding Due to HSP on Univariate Analysis

Variables	Univariate Logistic Regression			
	B Efficient	OR	95% CI	P-value
Gender	-0.024	0.976	0.607-1.570	0.921
>5y vs ≤5y	0.417	1.517	0.813-2.829	0.19
Delivery mode	-0.052	0.949	0.581-1.550	0.834
Arthralgia	-0.908	0.404	0.240-0.679	0.001**
Proteinuria	-0.403	0.668	0.374-1.193	0.172
Hematuria	-0.132	0.877	0.499-1.540	0.647
Duration of glucocorticoid use	0.030	1.030	1.018-1.042	< 0.001**
WBC	0.063	1.065	1.024-1.108	0.002**
Neutrophils%	0.029	1.029	1.012-1.047	0.001**
Neutrophil/Lymphocyte	0.133	1.142	1.051-1.241	0.002**
Hgb	0.006	1.006	0.986-1.026	0.539
PLT	0.002	1.002	1.001-1.004	0.007**
CRP	0.012	1.012	0.998-1.027	0.100
ESR	-0.080	0.923	0.889-0.959	< 0.001**
IgG	-0.146	0.864	0.785-0.952	0.003**
IgA	-0.148	0.862	0.618-1.204	0.384
IgE	0.001	1.001	1.000-1.001	0.160
C3	-1.470	0.230	0.074-0.714	0.011*
C4	-1.473	0.229	0.028-1.909	0.173
CD19%	0.155	1.122	1.077-1.168	<0.001**
CD3%	-0.044	0.957	0.932-0.982	0.001**
CD4%	-0.033	0.968	0.930-1.007	0.105
CD8%	-0.043	0.958	0.915-1.003	0.068
NK cell%	-0.095	0.909	0.848-0.976	0.008**

Notes: *P < 0.05, **P < 0.01.

Abbreviations: C, complement; CD, cluster of differentiation; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; NK, natural killer; Hgb, hemoglobin; Ig, Immunoglobulin; PCT, procalcitonin; PLT, blood platelet; WBC, white blood cell.

arthralgia (OR 0.404, P = 0.001), longer glucocorticoid use (OR 1.030, P < 0.001), increased leukocyte count (OR 1.065, P = 0.002), elevated neutrophils (OR 1.029, P = 0.001), and neutrophil/ lymphocyte percentages (OR 1.142, P = 0.002), PLTs (OR 1.002, P = 0.007), decreased ESR (OR 0.923, P < 0.001), low serum IgG levels (OR 0.864, P = 0.003), and elevated percentage of CD19+ cells (OR 1.122, P < 0.001), and compared to the CD3+ (OR 0.957, P = 0.001), lower percentage of NK cells (OR 0.909, P = 0.008), and lower C3 levels (OR 0.230, P < 0.05) compared to the control group. The multivariate logistic regression model revealed that only a decrease in arthralgia level, prolonged glucocorticoid use, an increase in neutrophil percentage, and a decrease in IgG, C3, and CD19+ cell percentages were associated with a higher risk of gastrointestinal bleeding, which was an independent predictor of the risk of gastrointestinal bleeding (Table 3). The area under the curve (AUC) for this model was 0.861 (Figure 1).

Role of Immunologic Response in HSP with GI Bleeding

The final multivariate logistic regression model included only serum C3 levels and CD19+ cell percentage to better elucidate the immunologic role in GI bleeding. ROC curve analysis revealed that this model could predict the development of GI bleeding in children with HSP, with an AUC of 0.721 (Figure 1, 95% CI: 0.632-0.811, P < 0.001). This suggests that immunologic mechanisms may be crucial for GI involvement in HSP patients.

Table 3 Risk Factors Associated with the Development of GI Bleeding Due to HSP on Multivariate Analysis

Variables	B Efficient	OR	95% CI	P value
Arthralgia	-1.853	0.157	0.046–0.539	0.003**
Glucocorticoid use	0.044	1.045	1.022–1.069	< 0.001**
WBC	0.035	1.035	0.916–1.170	0.576
N%	0.104	1.110	1.011–1.219	0.029*
Neutrophil/Lymphocyte	-0.349	0.706	0.431–1.154	0.706
PLT	0.001	1.001	0.996–1.007	0.681
ESR	-0.002	0.998	0.940–1.060	0.952
IgG	-0.170	0.844	0.719–0.991	0.038*
C3	-4.457	0.012	0.001–0.208	0.002**
CD19%	0.148	1.159	1.039–1.293	0.008**
CD3%	0.034	1.034	0.945–1.131	0.463
NK cell%	-0.105	0.900	0.799–1.013	0.082

Notes: *P < 0.05, **P < 0.01.

Abbreviations: N%, percentage of neutrophils; C, complement; CD, cluster of differentiation; ESR, erythrocyte sedimentation rate; NK, natural killer; Ig, Immunoglobulin; PLT, blood platelet; WBC, white blood cell.

Discussion

In this study, univariate logistic regression showed that decreased arthralgia, prolonged glucocorticoid use, increased white blood cell counts, elevated neutrophils and NLR, elevated PLTs, decreased ESR levels, decreased C3 levels,

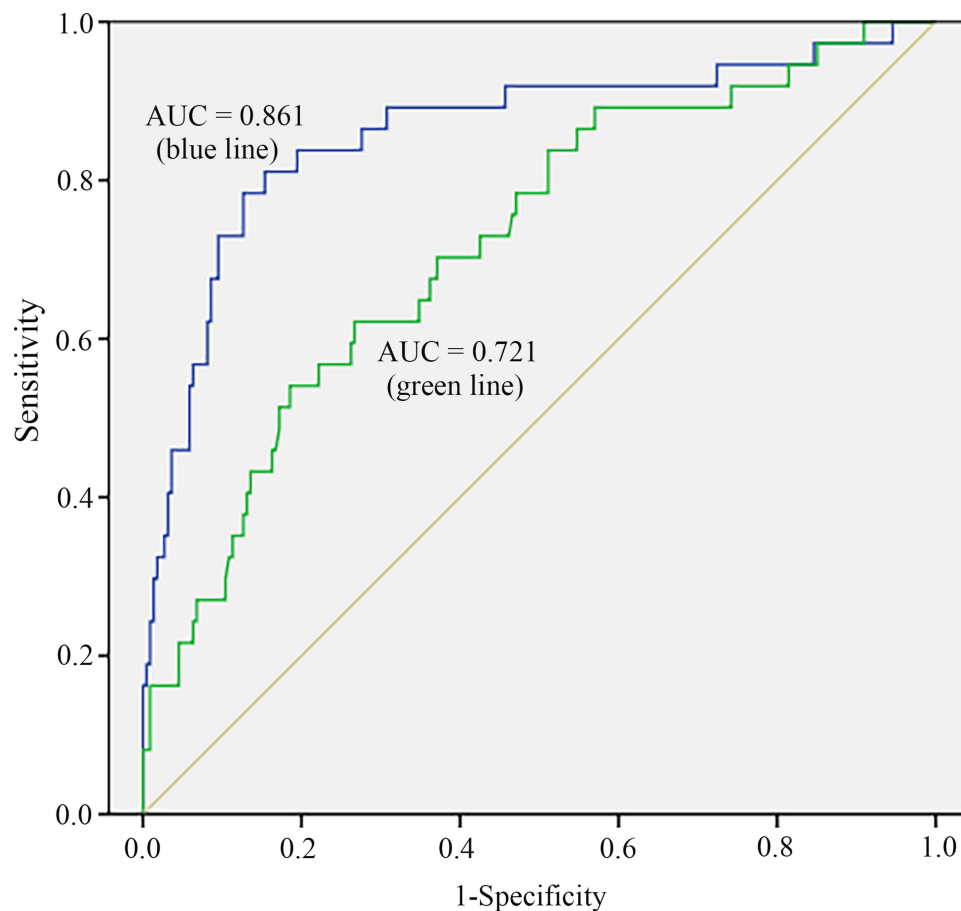


Figure 1 Predictive ability of the multivariate logistic regression model for developing GI bleeding. The AUC for the blue line (arthralgia, glucocorticoid use, N%, IgG, C3, and CD19%) is 0.861 (95% CI: 0.784–0.938, P < 0.001). The AUC for the green line (C3 and CD19%) is 0.721 (95% CI: 0.632–0.811, P < 0.001).

decreased serum IgG levels, increased CD19⁺ cell percentage, and decreased CD3⁺ and NK cell percentages were significantly associated with gastrointestinal bleeding risk in patients with HSP. However, multivariate regression analyses depicted that only a decrease in arthralgia level, an increase in glucocorticoid use, an increase in neutrophil percentage, a decrease in IgG and C3, and an increase in CD19⁺ cell percentage were independent predictors of gastrointestinal bleeding. Further analysis showed that the combination of C3 and CD19⁺ cell percentages predicted gastrointestinal bleeding in children with HSP.

A predictive model⁷ for GI bleeding risk in children with HSP revealed that eosinophils, high-sensitivity C-reactive protein, activated partial thromboplastin time, potassium, albumin, and IgE were independent predictors. Age at onset below six years, not receiving glucocorticoid therapy within 72 h of the onset of GI symptoms, hematochezia, and high D-dimer levels were associated with intussusception in pediatric HSP with GI involvement.¹⁸ A study found that the platelet-to-lymphocyte ratio and NLR can be reliable predictors of GI tract involvement in HSP patients but are not significantly associated with renal involvement.¹⁹ Additionally, an abdominal pain duration of more than seven days and a methylprednisolone dose of over 2 mg/kg increased gastrointestinal perforation in children with HSP.²⁰ The HSP in children with intermittent abdominal pain had a high risk of nephritis and severe GI bleeding. These patients should be followed up strictly with clinical and laboratory assessments, mainly during the first month of the disease course.²¹

There are inconsistent results in the literature regarding serum IgA, IgG, and IgM levels in children with HSP. Patients with HSP could have immune disorders outside the IgA compartment, and there could be interactions between IgA and other Igs, likely contributing to the higher likelihood of complications.²² Furthermore, HSP in children with GI symptoms who had elevated neutrophil counts, B lymphocyte percentage, and reduced IgG levels were associated with refractory GI involvement.⁶ Our study also demonstrated reduced IgG levels in HSP patients with GI bleeding than those without GI bleeding, indicating that humoral immune imbalance may contribute to HSP pathogenesis. However, the underlying mechanism remains unclear.

The reduced C3 levels were observed in the present HSP cases with GI bleeding. The complement system is involved in the pathogenesis of several autoimmune diseases, including HSP.²³ Lower C3 levels were associated with renal involvement and severity.⁹ Lin et al demonstrated that patients with HSP had a profound C4 reduction and moderate C3 reduction, indicating classical or lectin pathway activation.²⁴ However, the decrease in complement levels in HSP did not affect the prognosis of HSP and did not develop into systemic lupus erythematosus (SLE).²⁵ Glomerular deposition of complement factors, including C3 and C4, has been observed in most patients with HSP nephritis without C1q deposits, supporting the hypothesis of prevalent activation of the lectin pathway.²³ Urinary complement C3 and C4 levels were significantly higher in all children with HSP than in SLE patients,²⁶ indicating that reduced complement could be associated with urine loss. Although some patients with HSP have no detectable proteinuria, they still have hypoalbuminemia, probably due to intestinal protein loss.²⁷ These findings further suggest that, besides immune activation, gastrointestinal loss could contribute to hypocomplementemia.

Increasing evidence suggests that immune dysfunction is involved in HSP pathogenesis.^{9,14,24,28,29} This study showed that HSP in children with GI bleeding had a significantly increased serum CD19⁺ cell percentage than those without GI bleeding, consistent with prior studies. The HSP patients had a lower CD3⁺ lymphocyte percentage and higher CD19⁺ percentage than patients with infectious mononucleosis or *Mycoplasma pneumoniae* infection.²⁹ Additionally, circulating cytotoxic T lymphocytes and NK cells were activated, and their number in the glomeruli increased in HSP nephritis patients with severe proteinuria.²⁸ These results further revealed that different immune cell predominance may be disease-specific. Increased CD19⁺ cells in children with HSP were likely associated with GI bleeding.

Furthermore, it was intriguing to find a strong association between lower arthritis in HSP patients and GI hemorrhage. HSP can be categorized into simple cutaneous, arthritic, abdominal, renal, and mixed phenotypes, depending on the site of involvement and clinical presentation. Symptoms in patients with the articular form consist mainly of joint swelling and pain, commonly in the elbow, knee, and ankle,³⁰ which may be associated with exudates and hematomas. The most common complications in patients with the abdominal form include gastrointestinal bleeding, which may be related to the inflammatory response that occurs during the acute phase of HSP, and alterations in the PLT-activating factor and its acetyl hydrolase.^{31–33} In this study, using unifactorial and multifactorial logistic regression analyses, we found that children with arthralgia may be less likely to have concomitant gastrointestinal hemorrhage; however, the exact

mechanism remains unclear. Current studies and clinical practice cannot prove that arthralgia is not associated with gastrointestinal bleeding; however, we can determine that the direction of involvement may significantly differ.

Our study has some limitations. First, this retrospective study is based on a single-center hospital, and there may be selection bias. Future multicenter and prospective studies and recurrence follow-ups will help us better understand the HSP pathogenesis. Second, all laboratory tests were performed within 24 h of admission without dynamic monitoring. Finally, our GI bleeding classification relied mainly on the description of the medical history, perhaps missing some patients.

In conclusion, our study suggests that patients with IgAV who have reduced C3 levels or an increased CD19 lymphocyte proportion may have a higher risk of gastrointestinal bleeding. Specific immunologic features may be strongly associated with gastrointestinal bleeding in patients with HSP. Prospective multicenter studies on immune responses will help explain the pathogenesis of HSP.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

2022 In-hospital Science and Technology Innovation Fund of Sichuan Provincial Maternity and Child Health Care Hospital (CXPJ2022-01).

Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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