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ORIGINAL RESEARCH

Recurrence of Histiocytic Necrotizing Lymphadenitis in Children: A 10-year Multicenter Retrospective Study

Yong-Ping Xie[1,*], Yan-Wen Xu[2,*], Yan Li[1,*], Hu Zhang[3], Shan-Shan Xu[2], Mei-Na Lu[1], Yi-Ping Chen[3], Jian-Mei Tian[4], Xin-Fang Huang[5], Zhi-Feng Liu[6], Zhi-Gang Gao[7], Li-Su Huang[1]

[1]Department of Infectious Disease, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Infectious Disease, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; [3]Department of Pediatric Infectious Disease, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [4]Department of Infectious Disease, Children's Hospital of Soochow University, Suzhou, Jiangsu, People's Republic of China; [5]Department of Rheumatology, Shanghai East Hospital, Tongji University, School of Medicine, Shanghai, People's Republic of China; [6]Department of Gastroenterology, Children's Hospital of Nanjing Medical University, Nanjing, Jiangsu, People's Republic of China; [7]General Surgery Department, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhi-Gang Gao, General Surgery Department, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang, 310052, People's Republic of China, Email ebwk@zju.edu.cn;
Li-Su Huang, Department of Infectious Disease, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang, 310052, People's Republic of China, Tel/Fax +86 0571 86670978, Email lisuhuang@zju.edu.cn

Purpose: Histiocytic necrotizing lymphadenitis (HNL), or Kikuchi-Fujimoto disease, is prone to recurrence in children. However, the frequency and risk factors associated with recurrence remain unclear.

Patients and Methods: This study included all children with pathology-confirmed HNL from five hospitals over ten years (2013–2023). This study employed STROBE analysis to investigate the association between clinical characteristics and HNL, which was subsequently verified through in both a derivation group and a validation group. Initial clinical features were collected, and data were randomly divided into derivation and validation sets (3:2 ratio). Cox regression analysis identified risk factors, and receiver operating characteristic curves were used to develop a prediction model. Flow cytometry focused on assessing $CD4^+$ T-lymphocytes in lymphoid tissue.

Results: Of the 593 HNL cases, 88 (14.8%) experienced recurrence during a median follow-up of 3 years. Cumulative recurrence rates at the first, fifth, and ninth years were 8.7%, 20.0%, and 32.2%, respectively. Factors associated with recurrence included age ≤ 6-year-old (Hazard ratio [HR] 3.6, 95% confident interval [CI], 2.0–6.4), C-reactive protein > 16 mg/L (HR, 1.9, 95% CI, 1.0–3.6), blood $CD4^+$ T-lymphocytes ≤ 30% (HR, 4.4, 95% CI, 1.0–18.7), ferritin > 150 μg/L (HR, 2.3, 95% CI, 1.1–5.3) and platelets ≤ 200×10^9/L (HR 1.8, 95% CI, 1.0–3.2). The prediction model demonstrated areas under the curve of 0.81 for the derivation dataset and 0.77 for the validation dataset, classifying patients into low, medium, and high-risk categories, with corresponding recurrence rates of 5.2%, 19.0%, and 42.9%. Lower lymphoid $CD4^+$ T-lymphocyte counts were also observed in the recurrent group.

Conclusion: The recurrence of HNL increases over time. Key factors, including C-reactive protein (CRP) levels, $CD4^+$ T-lymphocyte counts, ferritin, platelets, and age at diagnosis may contribute to recurrence risk.

Keywords: histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto disease, recurrence, $CD4^+$ T-lymphocytes, ferritin, children

Introduction

Histiocytic necrotizing lymphadenitis (HNL), also known as Kikuchi-Fujimoto disease or Kikuchi disease, was once regarded as a rare condition.[1,2] However, recent research indicates that it may be more prevalent than previously understood, as HNL is now recognized as one of the most common causes of fever of unknown origin[3] and cervical lymphadenitis in children.[4,5]

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Studies show that HNL accounts for approximately 41.6% of cases involving benign cervical lymphadenopathy.[4] While most cases of HNL are mild and self-limiting, a minority can develop severe complications, such as hemophagocytic lymphohistiocytosis.[6] Recurrence of HNL is not uncommon, though reported rates vary significantly among adolescents and adults, ranging from about 3% to 42.4%.[7–9] This variation may be attributed to factors such as small sample sizes, short follow-up periods, a predominance of adult participants, and single-center designs. Consequently, the true recurrence rate of HNL in pediatric populations remains unclear. For children, recurrence often leads to multiple clinic visits and hospitalizations, which can adversely impact academic performance and mental health.[10] Furthermore, HNL has been suggested to represent a subclinical form of autoimmune disease, with recurrent cases potentially progressing to conditions like systemic lupus erythematosus (SLE).[11–13] HNL and certain autoimmune diseases, particularly SLE, share a complex and intricate relationship.[14] Autoimmune diseases may occasionally precede, develop subsequently, or sometimes be associated concurrently with Kikuchi-Fujimoto disease. Given these considerations, it is essential to investigate HNL recurrence in children, identify associated risk factors, and assess the potential for progression to autoimmune diseases.

Although HNL is a rare condition with limited global incidence data, studies from regions including China,[13] the Eastern Mediterranean,[15] Australia,[16] and the United States[17] provide valuable insights into its clinical features and prevalence in specific populations. Currently, there is limited research on the recurrence rate and risk factors for HNL, particularly in pediatric populations.[7,11,18,19] Most existing studies focus on adults, reporting varying recurrence rates that may not accurately reflect the situation in children. Potential risk factors for recurrence in adults include lymphopenia, prolonged recovery from lymphopenia, elevated anti-nuclear antibodies (ANA), and the presence of extra-nodal symptoms.[11,19] Interestingly, one small pediatric study indicated that elevated absolute lymphocyte counts, rather than lymphopenia, are linked to HNL recurrence. It is anticipated that the recurrence rate in adults is lower than in children, and the underlying pathophysiology may differ.[20] In light of these knowledge gaps, this multicenter retrospective cohort study aims to determine the rate of HNL recurrence in children, identify high-risk factors associated with the first recurrence, and develop predictive models to enhance our understanding of this condition.

Methods

Study Design and Population

Data for this multicenter retrospective study were collected from five major children's hospitals in Southeast China (Children's Hospital, Zhejiang University School of Medicine, Children's Hospital of Nanjing Medical University, Children's Hospital of Soochow University, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Yuying Children's Hospital of Wenzhou Medical University) between January 2013 and March 2023. All participating hospitals are tertiary facilities, each handling over a million pediatric outpatient visits annually across three provinces. The study focused on individuals under 18 years old with a pathology-confirmed diagnosis of histiocytic necrotizing lymphadenitis (HNL) from their initial episode. Exclusion criteria included coexisting autoimmune disorders at the time of HNL diagnosis, follow-up periods of less than one year, or incomplete symptom data.

The study was approved by the institutional review boards of aforesaid institutions and informed consent was waived.

Definition of HNL and Autoimmune Disorder Diagnosis

In this study, we identified both HNL and recurrent HNL through patients' medical records. Cases with identifiable alternative causes for lymphadenopathy were excluded, systematically ruling out potential factors such as infections, malignancies, and autoimmune conditions. All HNL cases received validation from a research board. A confirmed diagnosis of HNL required adherence to specific criteria which, by pathology examination, included irregular paracortical necrosis, the presence of abundant karyorrhectic debris, various types of histiocytes (including crescentic and foamy), thrombosed vessels, periadenitis, and a notable absence of neutrophils. Recurrence was defined as new episodes of febrile and painful lymphadenopathy occurring after the initial pathological diagnosis.[2,11,13,19,21,22] For recurrence to be considered, re-enlargement of the lymph nodes had to happen at least two weeks following clinical improvement; during this period, patients were afebrile, not on medications, had normalized blood counts, and exhibited a reduction in lymph

node size without tenderness. The primary outcome of interest was the first recurrence of HNL, and the interval was calculated from the clinical improvement of primary HNL to the onset of recurrence.

Diagnoses of systemic lupus erythematosus (SLE) were based on the revised 1997 criteria from the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA) and the 2019 American College of Rheumatology (ACR) criteria.[23–25] For juvenile idiopathic arthritis (JIA), we applied the 2001 and 2018 classification criteria from the JIA International League of Associations for Rheumatology (ILAR). Primary Sjögren's syndrome (pSS) was diagnosed according to the 2016 criteria established by the ACR and the European League Against Rheumatism (EULAR).[26–28]

Follow-Ups

The study protocol was consistent across the five participating medical centers. Before the study commenced, physicians and research staff received standardized training on data collection during site visits led by the principal investigator. Data management was facilitated through a research electronic data capture system. Following the initial pathologically confirmed diagnosis of histiocytic necrotizing lymphadenitis (HNL), patients were monitored using uniform questionnaires administered via telephone. Follow-up occurred every three to six months until January 31, 2024, or until patient death. Each recurrence was verified through medical records and confirmed by attending physicians and research staff.

Risk Factors

Potential risk factors for recurrence were identified based on prior investigations and expert input. Data from the initial hospitalization for HNL included: (1) basic characteristics such as age, sex, underlying conditions, and family history; (2) clinical signs, including lymph node characteristics (location, tenderness, laterality), pharyngeal congestion, tonsillar hypertrophy, hepatomegaly, and splenomegaly; (3) clinical symptoms such as fever (including high fever [a body temperature of 39°C or higher] and prolonged fever [a fever lasting 14 days or more]), flu-like symptoms, rash, arthralgia, myalgia, oral ulcers, vomiting, abdominal pain, and headaches; (4) laboratory findings encompassing various blood cell counts, inflammatory markers, blood lymphocytes subsets, and liver function tests; (5) ultrasound imaging of lymph nodes; (6) complications like encephalitis, haemophagocytic lymphohistiocytosis and thrombocytopenia; (7) results from immunohistochemical and flow cytometric analyses of lymph node tissues of children with HNL from Children's Hospital, Zhejiang University School of Medicine.

Flow Cytometry

Flow cytometry studies were performed on FACSCantoTM II flow cytometers (Becton Dickinson). We mainly focused on the data available on T-lymphocytes in this study. All antibodies were from BD Biosciences, including SK7 (CD3), SK3 (CD4) and SK1 (CD8). Data were analyzed by FlowJo 10.8.1. Lymphocytes were initially gated using $CD45^+$ events with low side scatter properties, then $CD3^+$ population was gated in CD3/SSC plot. $CD4^+$ and $CD8^+$ T cell subsets were further categorized based on CD4 and CD8 expression in $CD3^+$ population.

Statistical Analysis

The reporting of this study conforms to STROBE.[29] Descriptive statistics summarized the baseline characteristics of the study participants. Qualitative variables were presented as frequencies and percentages, and comparisons were made using the Chi-squared test or Fisher's exact test, as appropriate. For quantitative variables, medians and interquartile ranges (IQRs) were reported, with the Kruskal–Wallis H-test applied to non-normally distributed data and the Student's *t*-test for normally distributed data. Patients were initially randomized in a 3:2 ratio into two groups: the derivation group and the validation group. In the derivation group, the hazard ratio for recurrence of histiocytic necrotizing lymphadenitis (HNL) was analyzed using multivariate Cox models, including factors with $p < 0.05$ for further validation. Receiver-operating characteristic (ROC) analysis was conducted to identify significant factors from the Cox model, aiding in the development of a predictive model for recurrence. In the validation group, the Recurrence-Score based on the area under the curve (AUC) from the derivation group was evaluated through diagnostic testing, which generated positive and negative probability ratios, sensitivity, and specificity. Patients were categorized into low, medium, and high-risk groups

based on their Recurrence-Scores, and the cumulative recurrence rate for each category was calculated. We further validated the difference in the number of lymphocytes detected by flow cytometry inside the lymph nodes in the recurrent versus non-recurrent group. Statistical analyses were performed using R software version 4.3.2. This rigorous approach ensured a thorough evaluation of recurrence risk factors for HNL in children.

Results

Characteristics of Children with HNL

A total of 593 children (358 male, 235 female) participated in this study, with a follow-up period of up to 11 years (median: 34.6 months; IQR: 21.9–46.3 months) (Supplementary Figure 1 and Supplementary Table 1). The mean age of all patients was 9.7 years, ranging from 1.1 to 18 years. Most children were older than six years, while 68 (11.5%) were younger than six. Among the patients, 88 (14.8%) experienced recurrences, including 10 (1.7%) with multiple recurrences (Table 1). The cumulative recurrence rate in the first, third, fifth, and ninth years was 8.7%, 14.1%, 20.0%, and 32.2%, respectively (Figure 1A). Following their HNL diagnosis, seven (1.2%) children developed systemic autoimmune diseases: four patients with SLE, one patient with pSS, and two patients with JIA (Table 1). Notably, 71.4% (5/7) of patients with autoimmune conditions received their diagnoses within the first two years after HNL onset (Figure 1B). Three children with HNL used immunomodulators, 258 children with HNL had corticosteroids therapy, and none of them received hydroxychloroquine therapy. The recurrence rates were 12.3% in the corticosteroid group and 17.8% in the non-corticosteroid group ($p = 0.62$), indicating no statistical difference between the two (Supplementary Table 2).

Risk Factors for the Recurrence of HNL

The study utilized a 3-to-2 randomization process to form a derivation group of 356 patients and a validation group of 237 patients, both groups showing no significant differences in baseline characteristics at the time of initial diagnosis (Supplementary Table 1). In the derivation group, a higher proportion of recurrent patients were aged six or younger compared to non-recurrent patients (38.1% vs 12.4%). Cox regression analysis indicated that children with an onset age of six years or younger had over a threefold increased risk of recurrence compared to their older counterparts (Hazard Ratio [HR], 3.6; 95% Confidence Interval [CI], 2.0–6.4) (Table 2). Other clinical signs including fever, cutaneous rash,

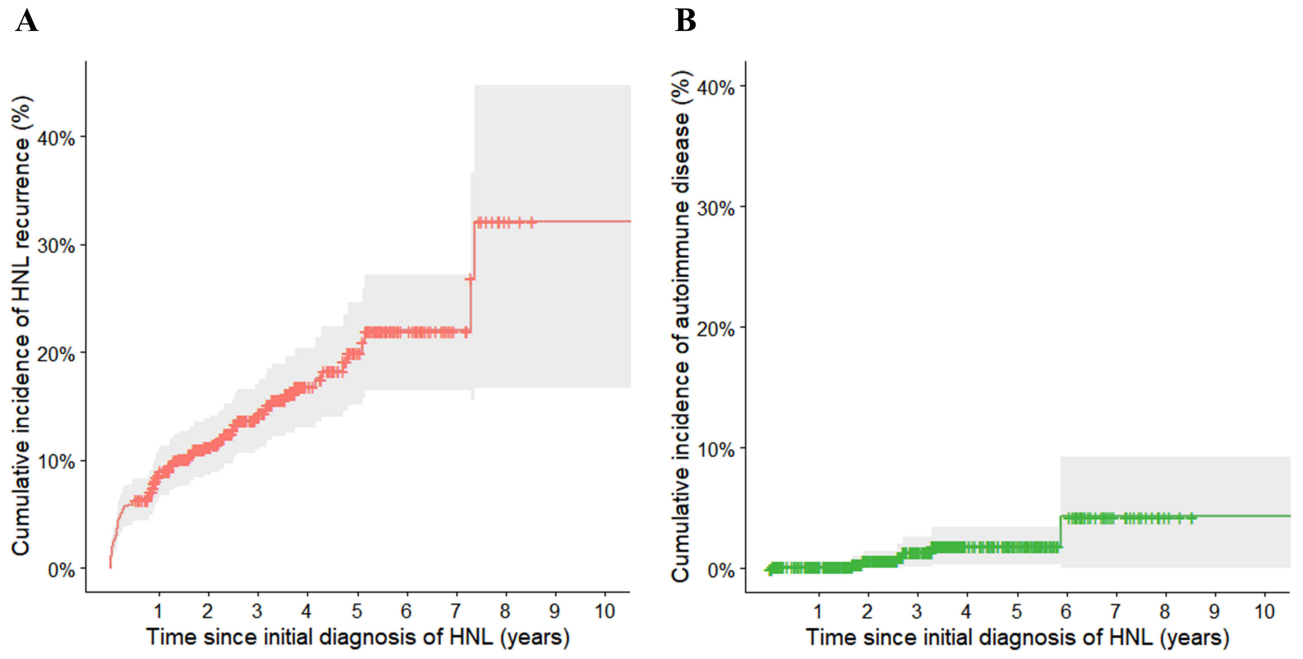

Figure 1 Cumulative event curves of recurrence (**A**) and autoimmune disease (**B**) in children with histiocytic necrotizing lymphadenitis (HNL).

Table 1 Baseline and Clinical Characteristics Stratified by Recurrence in Children with HNL (n=593)

Variables	Non-recurrence (n=505)	Recurrence (n=88)	*P*-value
Age group, years, n (%)			<0.01
≤6	44 (8.7)	24 (27.3)	
>6	461 (91.3)	64 (72.7)	
Age, Median (IQR), years	9.7 (7.8–12.1)	8.6 (5.8–11.7)	<0.01
Male, n (%)	302 (59.8)	56 (63.6)	0.50
Underlying diseases, n (%)	5 (1.0)	1 (1.1)	1.00
Family history, n (%)	4 (0.8)	2 (2.3)	0.22
Clinical symptoms, n (%)			
Fever	459 (90.9)	81 (92.0)	0.73
High fever (≥39°C)	385 (77.9)	67 (77.0)	0.85
Prolonged fever (≥2 weeks)	317 (62.8)	60 (68.2)	0.33
Cutaneous rash	79 (15.7)	18 (20.5)	0.26
Arthralgia	18 (3.6)	4 (4.5)	0.66
Headache	48 (9.5)	6 (6.8)	0.42
Myalgia	12 (2.4)	3 (3.4)	0.57
Oral mucosal ulceration	37 (7.3)	9 (10.2)	0.35
Bellyache	50 (9.9)	10 (11.4)	0.68
Vomit	42 (8.3)	5 (5.7)	0.40
Laboratory indicators, Median (IQR)			
Serum levels of C-reactive protein, mg/L	4.6 (2.8–11.1)	4.0 (3.6–17.4)	0.17
Absolute white blood cell counts, $\times 10^9$/L	3.6 (2.8–4.7)	3.9 (3.0–5.1)	0.11
Absolute neutrophil counts, $\times 10^9$/L	1.6 (1.1–2.2)	1.6 (1.3–2.2)	0.26
Percent lymphocytes, %	44.8 (36.9–52.5)	46.1 (35.4–52.7)	0.90
Absolute lymphocyte counts, ×10^9/L	1.6 (1.2–2.1)	1.7 (1.2–2.2)	0.20
Red blood cell counts, ×10^12/L	4.4 (4.1–4.6)	4.3 (4.1–4.6)	0.21
Hemoglobin, g/L	120.0 (111.0–127.0)	119.0 (112.0–127.0)	0.94
Platelet counts, $\times 10^9$/L	203.0 (164.0–249.0)	184.0 (152.0–229.5)	0.01
Procalcitonin, ng/mL	0.1 (0.1–0.2)	0.1 (0.1–0.1)	0.09
Percent $CD19^+$ B cells of lymphocytes, %	14.2 (10.8–18.8)	13.2 (10.6–17.6)	0.67
Percent $CD3^+$ cells of lymphocytes, %	72.1 (66.5–77.3)	68.2 (63.2–77.1)	0.09
Percent $CD4^+$ cells of lymphocytes, %	34.2 (29.3–39.1)	29.6 (24.7–34.5)	<0.01
Percent $CD8^+$ cells of lymphocytes, %	31.6 (27.1–36.0)	32.3 (27.1–37.3)	0.43
Percent $CD56^+$ NK cells of lymphocytes, %	10.3 (6.9–15.0)	11.7 (7.0–19.0)	0.23
Erythrocyte sedimentation rate, mm/h	28.0 (18.0–40.0)	30.0 (20.0–41.0)	0.33
Alanine aminotransferase, U/L	20.0 (13.0–41.0)	22.4 (13.0–47.4)	0.62
Aspartate aminotransferase, U/L	36.0 (29.0–54.0)	37.9 (29.0–56.0)	0.64
Alkaline phosphatase, U/L	141.0 (119.0–176.0)	138.5 (107.2–189.0)	0.85
γ-glutamyl-transferase, U/L	14.0 (11.0–19.0)	13.0 (10.0–19.0)	0.21
Lactate dehydrogenase, U/L	417.0 (326.0–563.0)	392.0 (321.0–536.5)	0.52
Ferritin, μg/L	221.1 (133.2–391.5)	269.4 (173.4–419.1)	0.11
Lymph node distribution, n (%)			
Cervical	490 (97.0)	88 (100.0)	0.10
Axillary	40 (7.9)	10 (11.4)	0.29
Inguinal	39 (7.7)	9 (10.2)	0.43
Abdominal	15 (3.0)	4 (4.5)	0.44
Supraclavicular	30 (6.0)	6 (6.8)	0.75
Multiple sites	89 (17.7)	19 (21.6)	0.38
Bilateral lymph node	166 (34.9)	24 (29.3)	0.32

(*Continued*)

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Table 1 (Continued).

Variables	Non-recurrence (n=505)	Recurrence (n=88)	*P*-value
Character of involved lymph node, n (%)			
Firm	52 (10.8)	10 (11.4)	0.87
Movable	434 (87.3)	76 (86.4)	0.70
Increased warmth	21 (4.2)	3 (3.4)	0.72
Hepatomegaly, n (%)	38 (7.6)	8 (9.1)	0.62
Splenomegaly, n (%)	43 (8.6)	15 (17.0)	0.01
Complications, n (%)			
Encephalitis	12 (2.4)	0 (0.0)	0.14
HLH	5 (1.0)	1 (1.1)	1.00
Thrombocytopenia	162 (32.9)	34 (42.0)	0.11
Time interval from symptom onset to biopsy, days, Median (IQR)	17.0 (12.0–24.0)	19.0 (13.2–25.0)	0.10
Corticoid, n (%)	212 (42.1)	46 (52.9)	0.06
Long-term outcomes, n (%)			
Autoimmune diseases	4 (0.8)	3 (3.4)	0.07

Abbreviations: HNL, histiocytic necrotizing lymphadenitis; HLH, hemophagocytic lymphohistiocytosis.

Table 2 Risk Factors Associated with Recurrence in Derivation and Validation Group of Children with HNL

Variables	Derivation Group (n=356)				Validation Group (n=237)			
	Recurrence/ Total (%)	Adjusted HR (95% CI)	*p*	AUC	Recurrence/ Total (%)	Adjusted HR (95% CI)	*p*	AUC
Age group, years				0.59				0.60
>6	39/314 (12.4)	1			25/211 (11.8)	1		
≤6	16/42 (38.1)	3.6 (2.0, 6.4)	<0.01		8/26 (30.8)	2.5 (1.1, 5.6)	0.03	
CRP, mg/L				0.48				0.59
≤16	36/283 (12.7)	1			20/182 (11.0)	1		
>16	13/56 (23.2)	1.9 (1.0, 3.6)	0.04		12/48 (25.0)	2.5 (1.2, 5.2)	0.01	
Percent $CD4^+$ cells of lymphocytes, %				0.65				0.64
>40	2/42 (4.8)	1			3/47 (5.6)	1		
30–40	17/127 (13.4)	2.8 (0.6, 12.1)	0.17		8/76 (10.5)	1.7 (0.5, 6.4)	0.43	
≤30	19/87 (21.8)	4.4 (1.0, 18.7)	0.05		14/59 (23.7)	4.3 (1.2, 15.0)	0.02	
Ferritin, μg/L				0.57				0.55
≤150	6/81 (7.4)	1			3/47 (6.4)	1		
>150	28/172 (16.3)	2.3 (1.1, 5.3)	0.04		21/134 (15.7)	2.4 (1.0, 6.8)	0.05	
Platelet, $\times 10^9$/L				0.54				0.65
>200	21/181 (11.6)	1			14/117 (12.0)	1		
≤200	32/173 (18.5)	1.8 (1.0, 3.2)	0.05		21/118 (17.8)	1.6 (1.0, 2.3)	0.05	

Abbreviations: HNL, histiocytic necrotizing lymphadenitis; CI, confidence interval; AUC, area under curve; CRP, C-reactive protein; $CD4^+$ percentage, the percentage of cluster of differentiation 4^+ T-lymphocytes; Hazard ratio adjusted by gender, underlying disease, family history, Adjusted HR, Adjusted hazard ratio; percent $CD4^+$ cells of lymphocytes, dividing absolute total lymphocyte counts by absolute $CD4^+$ T-lymphocyte counts.

arthralgia, oral mucosal ulcers, and lymph node features did not appear to differ between the recurrent and non-recurrent groups (Supplementary Table 1).

Specifically, those with C-reactive protein (CRP) levels exceeding 16 mg/L (23.2% vs 12.7%), ferritin levels above 150 mg/dL (16.3% vs 7.4%), and platelet counts at or below 200 × 10^9/L (18.5% vs 11.6%) showed increased

recurrence rates. The distribution of peripheral blood $CD4^+$ T-lymphocyte percentages ($CD4^+$ T-lymphocytes of total lymphocytes) among recurrent patients was as follows: ≤ 30% (21.8%), 30% to 40% (13.4%), and > 40% (4.8%) (Table 2). Higher CRP levels (HR, 1.9; 95% CI, 1.0–3.6), lower $CD4^+$ T-lymphocyte percentages (HR, 4.4; 95% CI, 1.0–18.7), elevated ferritin levels (HR, 2.3; 95% CI, 1.1–5.3), and lower platelet counts (HR, 1.8; 95% CI, 1.0–3.2) emerged as significant predictors of recurrence (Tables 1 and 2). Other laboratory indicators, such as white blood cell counts, ANA, lymphocyte counts, and alkaline phosphatase, did not show statistically significant differences between the recurrent and non-recurrent groups (Supplementary Tables 3 and 4). These five identified risk factors were similarly validated in the Cox regression analyses of the validation group (Table 2).

Prediction Model for HNL Recurrence

Based on the above five risk factors identified by cox regression analysis, we developed a prediction model for the recurrence of HNL. This model, termed the Recurrence-Score, is calculated using the following formula:

$$\begin{aligned}&\text{Recurrence} - \text{Score} = 0.67451 + (1.35846 \times \text{Age.6}) - \\&(0.02724 \times \text{Peripheral blood CD4} + \text{T} - \text{lymphocytes percentage}) \\&+(0.02969 \times \text{CRP level}) + (0.00022 \times \text{Ferritin level}) - (0.01244 \times \text{PLT count})\end{aligned}$$

(where Age.6 = 0 indicates age > 6 years and Age.6 = 1 indicates age ≤ 6 years).

In our derivation group, the AUC for the Recurrence-Score regarding HNL recurrence was 0.81 (95% CI, 0.71–0.92, Sensitivity: 0.85). In the validation group, the AUC was slightly lower at 0.77 (95% CI, 0.66–0.89, Sensitivity: 0.77). Among patients with complete data, the Recurrence-Score also achieved an AUC of 0.77 (95% CI, 0.65–0.88, Sensitivity: 0.72), aligning closely with the derivation and validation groups (Figure 2).

Recurrence Risk Stratification

Each patient's Recurrence-Score was calculated using the established formula. A higher score correlates with an increased likelihood of HNL recurrence. Recurrences were not seen in individuals with scores below −4, but over one-third of patients with scores above −1 experienced recurrences. Based on their Recurrence-Scores, we divided patients into three risk groups: low-risk (< −2), medium-risk (−2 to −1), and high-risk (≥ −1). In a cohort with complete data and a maximum follow-up of 11 years (median: 34.6 months, IQR: 21.9–46.3 months), the recurrence rates for the low-risk, medium-risk, and high-risk groups were 5.2%, 19.0%, and 42.9%, respectively, following the same trend as in the derivation and validation groups (Supplementary Table 5). The differences in recurrence risk across these groups were statistically significant ($p < 0.01$) (Figure 2). We also compared patients with complete data to those with missing variables and observed consistent results, even with the absence of certain parameters, particularly laboratory tests (Supplementary Tables 5, 6, and 7).

Validation of Low $CD4^+$ T-Lymphocyte Percentages in Recurrent Patients' Lymph Node Tissues

In our study of 438 peripheral blood samples, we included 63 from recurrence cases and 375 from non-recurrence cases, and found a significant difference in $CD4^+$ T-lymphocyte percentages, with medians of 50.7% (IQR: 44.6–56.6%) for non-recurrence cases compared to 42.6% (IQR: 36.9–50.6%) for recurrence cases. To further confirm the lower trend of low $CD4^+$ T-Lymphocyte percentages, we conducted flow cytometry on lymph node tissue from 93 children (11 with recurrence and 82 without) at Children's Hospital, Zhejiang University School of Medicine during 2022–2023. The characteristics of this subgroup were similar to those of the overall cohort (Supplementary Tables 8 and 9). The percentage of $CD4^+$ cells among lymphocytes was determined by flow cytometry assay in affected lymph nodes from both the recurrence group (Figure 3A) and the non-recurrence group (Figure 3B). Additionally, the percentage of $CD4^+$ T-lymphocytes in peripheral blood was assessed (Figure 3C). Representative flow cytometry plots (Figure 3A and B) and immunohistochemistry images (Figure 3D and E) revealed a significant reduction in $CD4^+$ T cells within the affected lymph nodes of patients with subsequent recurrence compared to those without recurrence. Specifically, in non-recurrence cases, $CD4^+$ T lymphocytes were densely distributed around the periphery of the necrotic area (Figure 3E),

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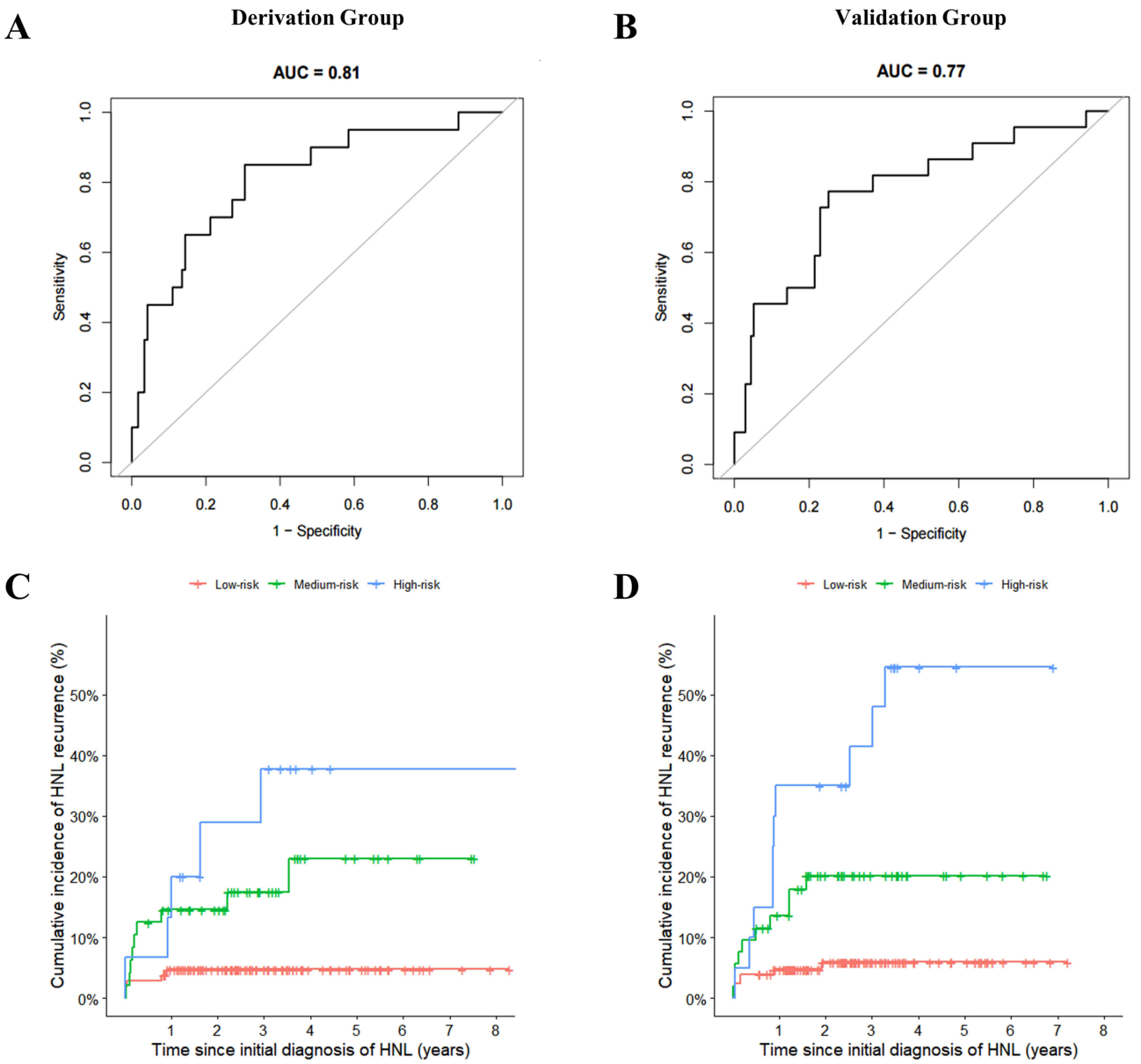

Figure 2 Receiver operating characteristic curves of predictive models for recurrence of histiocytic necrotizing lymphadenitis in derivation group (**A**) and validation group (**B**); cumulative risk of recurrence stratified by high-, medium-, and low-risk group according to the RecurrenceScore value in derivation group (**C**) and validation group (**D**).

whereas in recurrence cases, these cells were more scattered (Figure 3D). Significant differences were observed in the percentages of $CD4^+$ T cells in both lymph nodes and peripheral blood between the recurrence and non-recurrence groups (Figure 3C). Notably, the percentage of $CD4^+$ T-lymphocytes was significantly lower in the recurrence group, with a median of 24.2% (IQR:29.3–39.1%), compared to 29.6% (IQR: 24.7–34.5%) in the non-recurrence group. (Figure 3).

Discussion

In our multicenter study on histiocytic necrotizing lymphadenitis (HNL) in children, we found that the cumulative recurrence rate progressively increased over time. After nearly ten years of observation, around one-third of the patients experienced a recurrence. The clinical signs and symptoms during the initial episodes—such as fever, cutaneous rash,

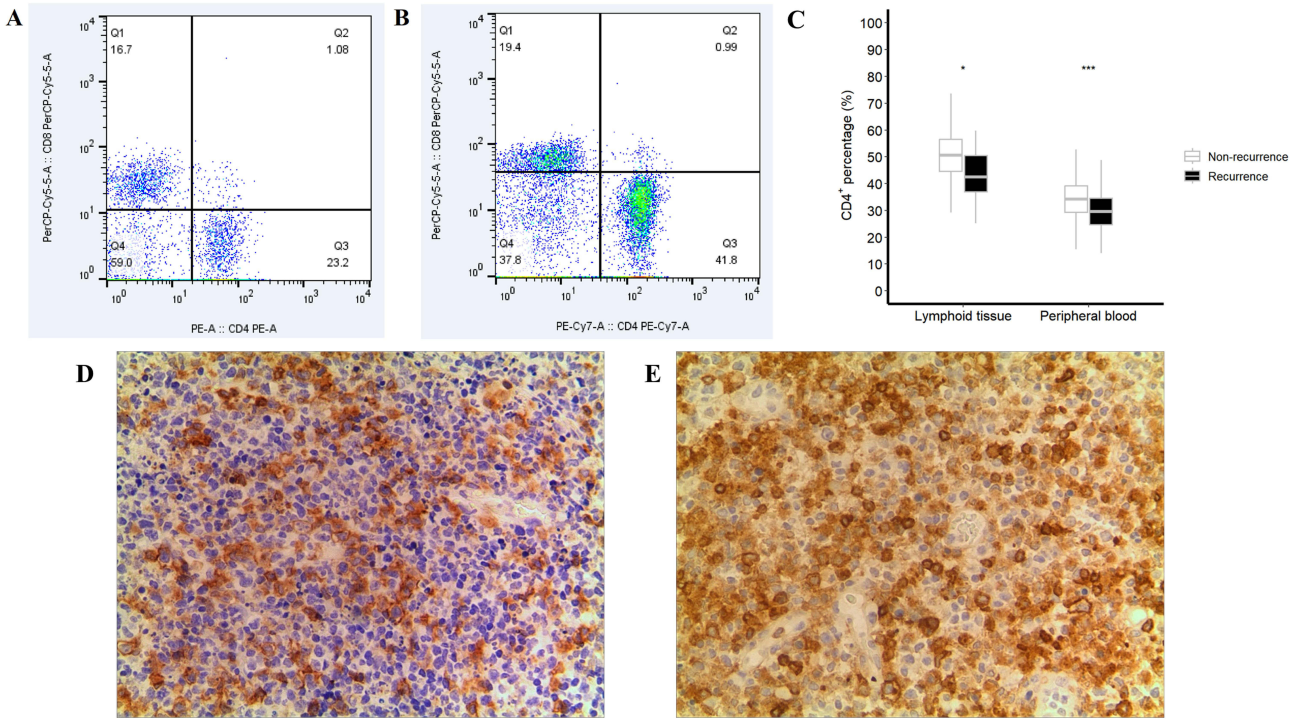

Figure 3 The percentage of $CD4^+$ cells among lymphocytes was determined by flow cytometry in affected lymph nodes from both the recurrence group (**A**) and the non-recurrence group (**B**). Additionally, the proportion of $CD4^+$ T-lymphocytes in both lymph nodes and peripheral blood was assessed (**C**). Representative flow cytometry plots (**A** and **B**) and Immunohistochemistry images (**D and E**) demonstrate a reduction in $CD4^+$ T cells within the affected lymph nodes in patient with subsequent recurrence compared to non-recurrence patient. In non-recurrence patient, $CD4^+$ T lymphocytes were densely distributed around the necrotic area periphery (**E**), whereas in recurrence cases, they were more scattered (**D**). Not only within individuals, but also between the recurrence and non-recurrence groups, significant differences were observed in the percentages of $CD4^+$ T cells in both lymph nodes and peripheral blood (**C**). (**E**) (IHC 200×) (**D**) (IHC *200). *$p<0.05$; ***$p<0.001$.

arthralgia, oral mucosal ulcers, and lymph node characteristics—were comparable in both recurrent and non-recurrent cases. A significant increased risk of recurrence, estimated to be 1.8 to 4.4 times higher, was observed in younger children (aged ≤ 6 years), those who presented with elevated CRP levels, lower $CD4^+$ T-lymphocyte percentages, higher ferritin levels, or lower platelet counts. The reason why younger children have a higher recurrence rate than children older than 6 years is not yet fully understood, we will continue to conduct related research in the future to further explore this issue. To assess this risk, we developed a prediction model called the Recurrence-Score, which demonstrated AUC greater than 0.75 in both validation and derivation groups. Notably, among individuals deemed high-risk according to the Recurrence-Score, the recurrence rates exceeded 40%.

Histiocytic necrotizing lymphadenitis (HNL) was initially identified in Asia but has since been observed across various racial and ethnic groups.[17,30,31] The prevalence of this condition varies significantly among different populations. For instance, a study conducted in the United States found that 75% of participants with Kikuchi disease were the Caucasian.[17] In Korea, HNL is recognized as one of the most common causes of cervical adenitis, affecting approximately one-third of individuals visiting outpatient clinics.[32] Historically, recurrence of HNL was considered rare. However, prior research on recurrence has primarily involved small sample sizes from Asia-Pacific countries, such as Korea and Singapore, and there is a lack of studies from other continents to determine whether these high recurrence rates are specific to Asia. Most existing studies focus on adults, with limited research on children. Our study revealed a cumulative recurrence rate reaching 30% over a decade of follow-up. Notably, we identified that 10 patients (1.7%) experienced multiple recurrences. Given their longer life expectancy post-diagnosis, children may be expected to have a higher cumulative recurrence rate than adults.

Our study found that seven (1.2%) of the children developed systemic autoimmune disorders, indicating a possibly higher prevalence linked to their young age. A Korean case series reported that 2.7% of patients with a mean age of 24 years developed autoimmune conditions following a diagnosis of Kikuchi disease.[11] In our cohort, these autoimmune

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diseases generally emerged within two years after the onset of HNL. To gain a clearer understanding of these trends, further research involving a larger sample size and extended follow-up is warranted.

The risk factors associated with the recurrence of HNL remain poorly understood. Common clinical presentations, such as fever, cervical lymphadenopathy, rash, arthritis, and hepatosplenomegaly, did not correlate with recurrence in our study population. While most patients with Kikuchi disease typically exhibit normal complete blood counts,[12] leukopenia has been found in more than 43% of cases in the studies.[13,22,33] Previous studies have suggested a potential connection between HNL recurrence and both elevated absolute lymphocyte counts[7] and lymphopenia (defined as an absolute lymphocyte count of less than 1500/mm³).[11] Our findings indicated that although total lymphocyte counts may not serve as reliable predictors, specific alterations in lymphocyte subsets may provide insights into HNL recurrence.

Histological examinations of biopsied lymph nodes reveal numerous T cells,[34] with immunohistochemistry showing apoptosis of $CD4^+$ T-lymphocytes and blastic transformation of $CD8^+$ T-lymphocytes. Notably, there is a significant decline in the percentage of $CD4^+$ cells in lymph node lesions during the second to fourth weeks, followed by a subsequent increase. This suggests that $CD4^+$ T-lymphocyte depletion could play a role in the pathogenesis of HNL.[35] However, the specific functions of $CD4^+$ T-lymphocytes in the lymph nodes of recurrent patients have yet to be fully explored. Our analysis of peripheral blood samples indicates that a decrease in $CD4^+$ T-lymphocytes to below 30% is associated with a recurrence rate more than four times higher than normal. Furthermore, we observed a more pronounced decline in the percentage of $CD4^+$ cells in the lymph node tissue of patients who experienced recurrence at initial diagnosis. Based on these observations, we propose that ongoing depletion of $CD4^+$ T-lymphocytes may significantly contribute to HNL recurrence.

This study represents the first effort to develop and evaluate a prediction model for the recurrence of histiocytic necrotizing lymphadenitis (HNL) in children. By combining data from five children's hospitals, we provide a detailed assessment of clinical presentations, laboratory characteristics, and recurrence patterns associated with HNL. The large sample size and multicenter design enhance the reliability of our findings. Our prediction model shows potential for future clinical application in forecasting first recurrences effectively.

This study has several limitations. First, pathology tests were conducted at individual centers without centralized review by a pathology lab. However, the participating centers are experienced referral institutions within their provincial regions, which helps mitigate this concern. Additionally, all pathology results and records were uniformly reassessed by our team of physicians including pathologists according to the study's diagnostic criteria prior to analysis. Second, there were instances of missing laboratory data for some patients, which could introduce bias into our findings. Due to the rarity of HNL, a retrospective approach was necessary, which may impact data quality, especially since no prospective or randomized controlled trials have been performed in this field. To address potential data limitations, we conducted sensitivity analyses that assessed the AUC and stratified cumulative recurrence rates for both patients with complete and incomplete data. These analyses revealed consistent trends related to risk factors for HNL. Third, our study did not require pathological confirmation for assessing recurrence, which may lead to potential false positives. Notably, there is no standardized definition of recurrence in existing literature or international guidelines. We identified children diagnosed with recurrence through a review of medical records and clinical information, systematically ruling out other causes of lymph node enlargement, including infections, autoimmune disorders, and malignancies. Additionally, in younger patients, where obtaining a second biopsy can be difficult, pathological assessment is often considered unnecessary. Furthermore, the confidence interval for the risk of recurrence associated with the percentage of $CD4^+$ lymphocytes is broad, indicating significant variability. While the odds ratio is significantly above 1, with a p-value of less than 0.05, this wide confidence interval may limit the predictive value of our findings. To improve the reliability of these results, future research should aim to conduct high-quality prospective cohort studies to narrow the confidence interval. Lastly, although our sample size was considerable, variability in follow-up duration complicates the interpretation of recurrence rates and the development of autoimmune diseases. Longer follow-up periods in future studies could yield clearer insights into outcomes for patients with histiocytic necrotizing lymphadenitis. Recognizing these limitations will inform future research efforts and enhance care for affected children.

Conclusion

During our extensive follow-up period spanning 11 years (median: 34.6 months; IQR: 21.9–46.3 months), our study found that recurrence of HNL may be linked to several factors, including younger children (aged ≤ 6 years), elevated CRP levels, a lower percentage of $CD4^+$ T-lymphocytes, increased ferritin levels, and reduced platelet counts. Given the high recurrence rate of HNL in children, implementing long-term follow-up, including lifelong monitoring, is essential to effectively monitor their condition.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by the institutional review boards of all participating institutions (Approval Number: 2023-IRB-0175-P-01).

The institutional review board (IRB) of our institution determined that parental consent for the review of medical records was not required for this retrospective study. This decision was based on the fact that the study only involved a review of pre-existing medical records, with no direct patient interaction or collection of additional data beyond what was already documented in the patient's medical history. The information was anonymized and kept confidential, ensuring that no personal identifying data was involved in the analysis.

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Disclosure

The authors have no conflict of interest to declare in this work.

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