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ORIGINAL RESEARCH

Risk Factors of Hemophagocytic Lymphohistiocytosis in Adults with Fever of Unknown Origin: A Retrospective Study

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Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a critical syndrome with a high mortality rate. In clinical practice, some patients with fever of unknown origin (FUO) can develop HLH, further complicating the diagnosis and treatment. However, studies on HLH in adults with FUO are limited. This study aimed to investigate the clinical characteristics of adult patients with FUO to facilitate the early identification of those at high risk of developing HLH.

Patients and Methods: We collected data from hospitalized patients with FUO between January 2014 and December 2020. Risk factors for HLH in adults with FUO were analyzed using univariate and multivariate analysis.

Results: A total of 988 patients with FUO were included in the study. The incidence of HLH in adults with FUO was 6.4%, with hematological tumors being the primary cause. Multivariate analysis indicated that skin rash and elevated alanine aminotransferase, total bilirubin, triglycerides, lactate dehydrogenase, and ferritin levels were independent risk factors for HLH in adults with FUO.

Conclusion: This study revealed the incidence rate, etiology distribution, and risk factors for HLH in adults with FUO. Comprehensive assessment of clinical and laboratory data at admission can assist in the early identification of FUO patients at risk for HLH.

Keywords: Hemophagocytic lymphohistiocytosis, fever of unknown origin, etiology distribution, risk factors

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe clinical syndrome that leads to multiple organ dysfunction, and its pathogenesis is not yet fully understood.[1,2] HLH was first formally recognized in 1991,[3] and the initial international treatment protocol (HLH-94) was developed in 1994.[4] Following further clinical investigations, the HLH-2004 protocol has been primarily used as diagnostic guidelines for HLH.[5,6]

HLH is categorized into two main types: (1) Primary hemophagocytic lymphohistiocytosis, which is mainly related to genetic mutations and susceptibility, and is commonly found in children;[7,8] (2) Secondary hemophagocytic lymphohistiocytosis, which can be triggered by various conditions, such as infectious diseases, malignancies, or autoimmune diseases, and is more common in adults.[9–11] HLH presents with a wide range of symptoms, and early manifestations are often nonspecific, involving multiple systems. The primary features of HLH include fever, organ enlargement, and hemocytopenia. Other common manifestations include hypertriglyceridemia, coagulation dysfunction, liver dysfunction, elevated inflammatory markers (especially ferritin), and nonspecific skin lesions.[1,5,12] The epidemiology of HLH varies across studies, and research on HLH in adults is less extensive compared with pediatric HLH studies.[13] It has been

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estimated that one in every 2000 adult admissions at tertiary medical centers involves HLH.[14] Recent studies have shown that the outcomes of secondary HLH are heterogeneous, with mortality rates ranging from 26.5% to 74.8%.[15] The overall mortality rate for adults with HLH has been reported as 41%,[12] but in critically ill adults, it can reach as high as 68%.[16–18]

Fever of unknown origin (FUO) is also a significant clinical challenge, with a similar etiology distribution and clinical manifestations to HLH.[19–23] In some cases, FUO may be the primary or sole manifestation of HLH.[24,25] Most studies on HLH with FUO are case reports, with highly heterogeneous study populations.[26–32] Additionally, many patients with HLH do not meet diagnostic criteria in the early stages, and some targeted tests [such as pathological tests or natural killer (NK) cell activity tests] cannot be performed immediately or are unavailable.[10]

Currently, no single clinical sign or laboratory parameter can definitively diagnose HLH. Given the limited data on the incidence and risk factors of HLH in adults with FUO, this study aimed to compare early parameters between FUO patients with and without a subsequent HLH diagnosis to identify predictors of HLH.

Materials and Methods

Study Design and Population

This study was conducted at Tongji Hospital, the largest teaching hospital in central China. Clinical information was collected from hospitalized patients with FUO who were admitted to the Department of Infectious Diseases from January 2014 to December 2020. The diagnostic criteria for classic FUO are as follows:[20,33] (1) Temperature above 38.3°C recorded on several occasions; (2) Fever lasting at least 3 weeks; (3) Etiology undetermined despite investigations during three outpatient visits or a 3-day hospital stay. The diagnostic criteria for HLH are based on the 2004 hLH Diagnostic Criteria, requiring at least five of the following eight criteria to be met during hospitalization:[5] (1) Fever; (2) Splenomegaly; (3) Cytopenia affecting at least two of the three cell lineages [hemoglobin (Hb) < 90 g/L, platelets (PLT) < 100 × 10□/L, and/or neutrophils (N) < 1.0 × 10□/L]; (4) Hypofibrinogenemia (fibrinogen < 1.5 g/L) and/or hypertriglyceridemia (triglycerides ≥ 3.0 mmol/L); (5) Hyperferritinemia (ferritin ≥ 500 μg/L); (6) Elevated soluble interleukin-2 receptor (IL-2R ≥ 2400 U/mL); (7) Low or absent NK cell activity; and (8) Hemophagocytosis in the bone marrow, spleen, or lymph nodes. Exclusion criteria: (1) Failure to meet the classical FUO diagnostic criteria; (2) Age under 18 years; (3) Pregnancy; and (4) Patients with incomplete clinical information or discharged within 48 hours.

Data Collection

Data were collected from both the HLH group and the non-HLH group. This included demographic information, highest body temperature, underlying diseases, main clinical signs, and laboratory indicators within 48 hours of admission, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), triglycerides, white blood cell (WBC) count, neutrophil (N) count, lymphocyte (L) count, hemoglobin (Hb), platelets (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), C-reactive protein (CRP), ferritin, and interleukin-6 (IL-6).

Statistical Analysis

Data variables were presented as medians (M) and interquartile ranges (IQR). Quantitative variables were first tested for normality. If normally distributed, they were analyzed using a *T*-test; otherwise, the rank sum test was used. Categorical variables were presented as numbers (%) and compared using the chi-square test or Fisher's exact test. Univariate analysis was performed to assess the relevant risk factors for HLH in adults with FUO. Variables with $P < 0.1$ from the univariate analysis were included in the multivariate logistic regression analysis. The discriminatory power of statistically significant parameters was assessed using the area under the receiver operating characteristic (ROC) curve. All P-values were two-tailed, with $P < 0.05$ considered statistically significant. All analyses were performed using SPSS 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

Results

Distribution of HLH in Adults with FUO

In this study, a total of 988 patients with FUO were enrolled from January 2014 to December 2020. Among them, 6.4% (63/988) developed HLH, as shown in Table 1. Of these, 44.4% (28/63) were associated with hematologic tumors, with non-Hodgkin lymphoma being predominant (71.4%, 20/28). In 28.6% (18/63), HLH was associated with infections, primarily Epstein-Barr virus (EBV) infections (38.9%, 7/18). Additionally, 17.5% (11/63) were associated with non-infectious inflammatory diseases (NIID), and 9.5% (6/63) had undiagnosed diseases.

Clinical Characteristics and Risk Factors of HLH in Adults with FUO

We compared the data from HLH patients with FUO (n=63) to those without HLH (n=925), as presented in Table 2. Univariate analysis showed that younger age, higher body temperature, skin rash, polyserositis, hepatomegaly, and

Table 1 Distribution of HLH in Adults with FUO

Diagnosis	N	N%
Infectious diseases	18	28.6%
Bacterial infection	6	9.5%
Tuberculosis	3	4.8%
Viridans streptococci	2	3.2%
Stenotrophomonas maltophilia	1	1.6%
Viral infection	7	11.1%
EBV	6	9.5%
EBV + CMV	1	1.6%
Fungal infection	1	1.6%
Aspergillus flavus	1	1.6%
Unknown pathogenic infection	4	6.3%
NIID	11	17.5%
AOSD	6	9.5%
SLE	5	7.9%
Neoplastic diseases	28	44.4%
Lymphoma	20	31.7%
Mature B-cell lymphoma	13	20.6%
Mature T-cell or NK cell neoplasm	7	11.1%
Leukemia	7	11.1%
Multiple myeloma	1	1.6%
Undiagnosed diseases	6	9.5%

Abbreviations: EBV, Epstein-Barr virus; CMV, Cytomegalovirus; NIID, non-infectious inflammatory diseases; AOSD, Adult-onset Still's disease; SLE, Systemic lupus erythematosus.

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Table 2 Univariate Analysis of Risk Factors for HLH in Adults with FUO

Variable	HLH Group (N=63)	Non-HLH Group (N=925)	P-Value
Basic information			
Male	29 (46%)	500 (54.1%)	0.217
Age (yrs)	45 (25, 56)	50 (37, 61)	**0.003**
Highest temperature (°C)	39.7 (39, 40)	39.4 (39, 40)	**0.001**
Underlying diseases			
Hypertension	6 (9.5%)	124 (13.4%)	0.378
Cardiovascular disease	1 (1.6%)	31 (3.4%)	0.691
Diabetes	3 (4.8%)	66 (7.1%)	0.646
Chronic pulmonary disease	1 (1.6%)	16 (1.7%)	1
Chronic liver disease	4 (6.3%)	82 (8.9%)	0.493
Chronic kidney disease	0 (0%)	31 (3.4%)	0.27
Clinical manifestation			
Chill	28 (44.4%)	368 (39.8%)	0.465
Muscle/joint pain	16 (25.4%)	288 (31.1%)	0.34
Skin rash	21 (33.3%)	131 (14.2%)	**< 0.001**
Polyserositis	14 (22.2%)	60 (6.5%)	**< 0.001**
Enlarged lymph nodes	33 (52.4%)	372 (40.2%)	0.057
Enlarged liver	11 (17.5%)	36 (3.9%)	**< 0.001**
Enlarged spleen	41 (65.1%)	253 (27.4%)	**< 0.001**
Laboratory indexes			
ALT (g/L)	46 (24, 136)	25 (14, 47)	**< 0.001**
AST (g/L)	58 (36, 215)	27 (18, 50)	**< 0.001**
TBil (umol/L)	12.9 (8, 51)	9.2 (6.5, 13.5)	**< 0.001**
Triglyceride	2.18 (1.48, 3.26)	1.17 (0.86, 1.63)	**< 0.001**
WBC ($\times 10^9$/L)	4.45 (2.05, 7.84)	7.2 (4.73, 10.44)	**< 0.001**
N ($\times 10^9$/L)	2.71 (1.13, 6.05)	5.25 (3.05, 8.46)	**< 0.001**
L ($\times 10^9$/L)	0.77 (0.35, 1.42)	1.07 (0.75, 1.52)	**< 0.001**
Hb ($\times 10^{12}$/L)	104 (84, 117)	107 (93, 121)	**0.026**
PLT ($\times 10^9$/L)	97 (51, 198)	224 (143.5, 315.5)	**< 0.001**
PT(s)	15 (14, 16.9)	14.6 (13.9, 15.5)	**0.003**
APTT(s)	45 (40.4, 54.3)	43.9 (39.3, 49.3)	**0.044**
Fibrinogen (g/L)	3.33 (1.57, 5.07)	5.38 (3.86, 6.77)	**< 0.001**
LDH/10^2 (U/L)	6.78 (4.52, 13.31)	2.27 (1.68, 3.73)	**< 0.001**

(*Continued*)

Table 2 (Continued).

Variable	HLH Group (N=63)	Non-HLH Group (N=925)	P-Value
ESR (mm/H)	20.5 (7.75, 54.25)	53.5 (23, 88)	**< 0.001**
PCT (ng/mL)	0.39 (0.19, 1.21)	0.18 (0.08, 0.48)	**< 0.001**
CRP (mg/L)	64.1 (28.6, 92.9)	70.4 (30.7, 120.6)	0.224
Ferritin /10^3 (μg/L)	4.82 (1.62, 15.93)	0.69 (0.36, 1.58)	**< 0.001**
IL-6 (pg/mL)	54.76 (22.65, 90.24)	36.55 (15.85, 88.92)	0.164

Note: Bold text indicates statistical significance with P<0.05.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; WBC, white blood cell; N, neutrophils; L, lymphocyte; Hb, hemoglobin; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin 6.

splenomegaly were significantly more common in the HLH group. Additionally, compared with non-HLH patients, those with HLH were more likely to exhibit lower hemocyte levels, liver dysfunction, and coagulation abnormalities and elevated triglyceride, LDH, ferritin, and PCT levels, but lower ESR levels.

Sex and variables with $P < 0.1$ were included in the multivariate regression analysis (Table 3). Skin rash, elevated ALT, TBil, triglyceride, LDH, and ferritin levels were independent risk factors for HLH development in adults with FUO. ROC curves based on these six predictors are shown in Figure 1. The area under the ROC curve (AUC) was 0.889 (95% confidence interval, 0.846–0.932), with a sensitivity of 84.2% and a specificity of 82.3%.

Table 3 Multivariate Logistic Analysis of Risk Factors for HLH in Adults with FUO

Variables	β-Coefficient	OR (95% Confidence Interval)	P-Value
Sex	0.111	1.117 (0.53–2.354)	0.771
Age	−0.018	0.982 (0.958–1.006)	0.141
Highest temperature	−0.038	0.963 (0.577–1.607)	0.884
Skin rash	0.959	2.608 (1.114–6.107)	**0.027**
Polyserositis	0.569	1.766 (0.645–4.834)	0.268
Enlarged lymph nodes	0.202	1.224 (0.59–2.537)	0.587
Enlarged liver	0.695	2.004 (0.599–6.711)	0.259
Enlarged spleen	0.325	1.384 (0.622–3.079)	0.426
ALT	0.003	1.003 (1–1.005)	**0.041**
AST	−0.004	0.996 (0.992–1)	0.056
LDH/10^2	0.112	1.119 (1.031–1.214)	**0.007**
Triglyceride	0.44	1.552 (1.169–2.06)	**0.002**
TBil	0.015	1.016 (1.004–1.027)	**0.009**
WBC	−0.092	0.912 (0.79–1.053)	0.208
N	0.027	1.027 (0.915–1.153)	0.652

(*Continued*)

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Table 3 (Continued).

Variables	β-Coefficient	OR (95% Confidence Interval)	P-Value
L	−0.15	0.861 (0.507–1.462)	0.579
Hb	−0.021	0.979 (0.957–1.001)	0.058
PLT	−0.002	0.998 (0.994–1.003)	0.513
PT	−0.155	0.856 (0.713–1.029)	0.097
APTT	−0.021	0.979 (0.938–1.022)	0.338
Fibrinogen	−0.127	0.881 (0.623–1.245)	0.473
ESR	0.001	1.001 (0.984–1.018)	0.921
Ferritin/10^3	0.036	1.036 (1–1.073)	**0.048**
PCT	0.014	1.014 (0.984–1.046)	0.368

Note: Bold text indicates statistical significance with P<0.05.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; WBC, white blood cell; N, neutrophils; L, lymphocyte; Hb, hemoglobin; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.

Discussion

HLH is a challenging syndrome to diagnose and treat, triggered by various factors. In this study, we identified six factors —skin rash, elevated ALT, TBil, triglyceride, LDH, and ferritin levels—as significant predictors of HLH in adults with FUO.

Current studies show wide variability in the reported incidence of HLH. While the incidence is lower among general inpatients (including both adults and children), it is higher among critical inpatients and/or patients with hyperferritinemia.[34–36] Wang et al[37] reported that 20.2% of adults with FUO developed HLH. In our study, the incidence was 6.4%, indicating that the incidence of HLH in adults is strongly influenced by the study setting.

Current studies have shown that multiple factors can trigger HLH.[1,2,38,39] A systematic review showed that the most common trigger of HLH in Asia was neoplastic diseases (especially lymphoma), while infections (particularly EBV)

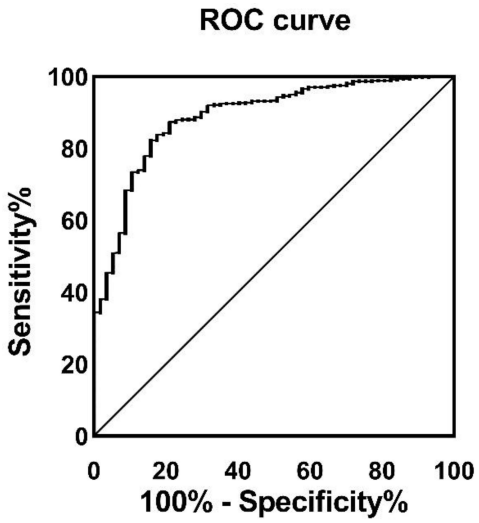

Figure 1 The area under of the ROC curve (AUC = 0.889, P < 0.001).

were more prevalent triggers in Europe and America. Considering the etiology similarity between FUO and HLH, the presentation of HLH with FUO has been reported in a few case reports.[26,30,31,40] Among these causes of FUO, HLH is most likely to be induced by neoplastic diseases (especially lymphoma), infectious diseases (especially tuberculosis and EBV infection), and NIID (particularly Adult-onset Still's disease and Systemic lupus erythematosus). Our findings are consistent with these studies, lymphoma is the main triggering factor of HLH with FUO, followed by infections and NIID. The proportion of unknown triggering factors varied considerably (from 3.7% to 35.8%).[12,37,41] Our findings align with these studies, with 9.5% of patients lacking identifiable triggering factors, similar to findings in patients with FUO.[37] This might be due to differences in the study population.[19,42] In addition, some studies suggest that a reasonable approach to reducing bias in FUO cases may be to abandon time-dependent criteria and adopt quality-based criteria that may vary in countries, for which there is no consensus.[20,43,44] This also partly explains the differences between the studies.

Numerous risk factors for HLH have been identified.[10] Fever, splenomegaly, hepatomegaly, skin lesions, hemocytopenia, liver dysfunction, coagulation abnormalities, and elevated inflammatory markers are common in HLH.[2,45–48] Similar to these findings, these manifestations were more common in patients with HLH than in non-HLH patients at earlier stages. Our study showed that the median age at onset of HLH was 45, whereas Wang et al[37] reported a median age of 57, likely due to differences in the proportion of neoplastic diseases (44.4% vs 55.3%). We identified skin rash and elevated ALT, TBil, triglyceride, LDH, and ferritin levels as independent risk factors for HLH development in adults with FUO, similar to the findings in adult patients with HLH.[37,49,50] It's worth noting that skin rash is an independent risk factor for HLH in adult FUO patients. Skin rash is not an important clinical feature of HLH, but may be a clinical manifestation of the primary disease that induces HLH.[32,40,51] This result may be potentially due to differences in the study population, highlighting the need for context-specific analyses. No single indicator is specific for diagnosing HLH.[50,52] Therefore, the area under ROC curve that were drawn based on six independent risk factors was higher than that for individual factors.

Some limitations of this study should also be acknowledged. Firstly, being a single-center study, the results may not be generalizable. Secondly, the relatively small number of adults with HLH may reduce the discriminatory power of some variables. Thirdly, the lack of follow-up could have influenced the results. Despite these limitations, this study is one of the few clinical studies focused on HLH in adults with FUO as far as our knowledge. Moreover, combining clinical symptoms with early laboratory indicators could help clinicians identify HLH in adults with FUO and reduce mortality.

Conclusions

In conclusion, the incidence of HLH in adults with FUO was 6.4%, with hematological tumors (especially lymphoma) being the primary cause. Skin rash and elevated ALT, TBil, triglyceride, LDH, and ferritin levels were independent risk factors for HLH development in adults with FUO. As timely diagnosis for HLH is crucial, highlighting the need for better prediction tools to improve prognosis in patients with FUO.

Abbreviations

HLH, Hemophagocytic lymphohistiocytosis; FUO, fever of unknown origin; NIID, non-infectious inflammatory diseases; EBV, Epstein-Barr virus; AOSD, Adult-onset Still's disease; SLE, systemic lupus erythematosus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; WBC, white blood cell; N, neutrophils; L, lymphocyte; Hb, hemoglobin; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time, fibrinogen; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; CRP, C-reactive protein; ferritin; IL-6, interleukin 6.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20230425). Informed consent was waived by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology because of the retrospective design. This retrospective study involved no personally identifying information, posed minimal risk to the subjects without violating their rights or interests, and could not proceed if informed consent was required. Upon obtaining the data, the researcher assumes responsibility for maintaining confidentiality by replacing personal information with anonymous identifiers, and when publishing or presenting findings, aggregate data should be used to protect the privacy of subjects.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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