ORIGINAL ARTICLE

Predicting Secondary Hemophagocytic Lymphohistiocytosis in Adult Patients with Scrub Typhus and Its Prognostic Significance

Suresh Selvam[1], Akshit Tuli[2], Kumar P Yuvasai[3], Shashikant Saini[4], Sathvik R Erla[5], Jyotdeep Kaur[6], Manisha Biswal[7], Navneet Sharma[8], Ashok K Pannu[9]

Received on: 22 May 2024; *Accepted on:* 29 July 2024; *Published on:* 31 August 2024

Abstract

Objective: Secondary hemophagocytic lymphohistiocytosis (sHLH) is an increasingly recognized complication in patients with scrub typhus, potentially contributing to substantial mortality despite appropriate antibiotic treatment. This study aims to determine the prevalence and prognosis of sHLH and identify diagnostic factors in adult patients with scrub typhus in North India.

Methods: This prospective cohort study was conducted at PGIMER, Chandigarh, from August 2021 to November 2023. sHLH was defined as an HScore of 200 or above. The diagnostic performance of biomarkers such as ferritin, fibrinogen, triglycerides, and C-reactive protein was assessed through receiver operating characteristic curve analysis, evaluating area under the curve (AUC), sensitivity, and specificity.

Results: Out of 150 patients (mean age 39 years, 54% female), 28 (18.7%) were diagnosed with sHLH. Those presenting with high-grade fever, seizures, high pulse rate, hepatomegaly, splenomegaly, cytopenia, and significant hepatic dysfunction were more likely to have sHLH. Ferritin demonstrated the highest diagnostic utility (AUC 0.83), compared to fibrinogen (AUC 0.72), triglyceride (AUC 0.67), and C-reactive protein (AUC 0.69). The optimal cutoff for ferritin was 2000 ng/mL, with a sensitivity of 90% and a specificity of 66%. Higher ferritin thresholds (6000 ng/mL and 10000 ng/mL) increased specificity to 88% and 95%, respectively. Patients with sHLH often presented with multi-organ failure, necessitating mechanical ventilation and vasopressor support. In-hospital mortality was significantly higher in sHLH patients than in those without (21.4% vs 6.6%, $p = 0.025$).

Conclusion: Early detection of sHLH using the HScore and ferritin significantly influences the management of scrub typhus, underscoring the necessity for tailored therapeutic strategies to improve patient outcomes.

Keywords: Biomarkers, Diagnostic accuracy, Ferritin, Hemophagocytic lymphohistiocytosis, Prognosis, Scrub typhus, Secondary hemophagocytic lymphohistiocytosis.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24787

Highlights of the Study

- A significant proportion of patients with scrub typhus present with secondary hemophagocytic lymphohistiocytosis (sHLH) in the emergency department.
- Among various biomarkers, ferritin demonstrates the highest diagnostic accuracy for predicting sHLH, surpassing fibrinogen, triglyceride, and C-reactive protein.
- The presence of sHLH in scrub typhus patients is associated with adverse clinical outcomes.

Introduction

Scrub typhus, a mite-borne rickettsial infection caused by *Orientia tsutsugamushi*, is a major public health problem that extends beyond its traditional endemic regions of Asia and northern Australia, the so-called Tsutsugamushi Triangle.[1,2] This life-threatening infection results in about one million cases each year with about 10–15% mortality in the hospitalized patients.[1–4] The disease typically presents as an acute febrile illness with myalgia, skin rash, eschar, dyspnea, hepatosplenomegaly, or thrombocytopenia; however, in about one-third of cases, it may rapidly progress to severe organ dysfunction, such as acute respiratory distress syndrome, acute kidney injury, acute brain dysfunction, acute liver injury, disseminated intravascular coagulation, myocarditis, or circulatory shock.[3–6]

[1–5,8,9]Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[6]Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[7]Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding Author: Ashok K Pannu, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India, Phone: +91 9914291115, e-mail: gawaribacchi@gmail.com

How to cite this article: Selvam S, Tuli A, Yuvasai KP, Saini S, Erla SR, Kaur J, *et al*. Predicting Secondary Hemophagocytic Lymphohistiocytosis in Adult Patients with Scrub Typhus and Its Prognostic Significance. Indian J Crit Care Med 2024;28(9):823–831.

Source of support: Nil

Conflict of interest: None

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory syndrome characterized by pathological immune dysregulation and excessive cytokine release (cytokine storm), leading to widespread tissue inflammation and affecting multiple organ systems.[7,8] This results in a sepsis-like syndrome with multiorgan dysfunction. Initially diagnosed and categorized in

children, primary HLH is due to a rare genetic disorder of cytotoxic T cells and natural killer cells. However, secondary HLH (sHLH) has increasingly been recognized in adults, where it is caused by immune hyperactivation initially triggered by an infectious, autoimmune, or neoplastic process.[7–12] Infections are the most prevalent triggers of sHLH, with viral infections, such as members of the human herpesvirus family, particularly Epstein–Barr virus, being the most common.[7–11] Rickettsial infections, such as scrub typhus, remain a common cause in endemic regions.[13]

Although heightened awareness and the prompt initiation of appropriate antibiotics have improved outcomes of scrub typhus, substantial mortality, and morbidity persist in low-middle-income countries (LMICs) despite the use of combination anti-rickettsial antibiotics.[4,5] Besides advanced organ failure at presentation, unrecognized sHLH might be associated with a poor prognosis in scrub typhus patients, necessitating rapid diagnosis and timely immunomodulation therapy.[7] However, early detection of sHLH is challenging due to its non-specific features, which overlap with those of scrub typhus, including fever, cytopenia, hepatomegaly, splenomegaly, and hepatic dysfunction. Furthermore, comprehensive data on scrub typhus-associated sHLH in adults is sparse, and mostly limited to case reports or small series.[13,14] Markers of immune hyperactivation or hyperinflammation, such as ferritin, have shown utility in predicting and assessing infection-associated sHLH.[7,15] This study aims to determine the prevalence and prognosis of sHLH and to identify diagnostic factors at presentation by evaluating the baseline clinical features, laboratory parameters, and outcomes of adult patients with scrub typhus in North India.

Methods

Study Design and Oversight

This prospective cohort study was conducted from August 2021 to November 2023 at the Acute Care and Emergency Medicine Unit, Department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. We included consecutive patients aged 13 years or older diagnosed with scrub typhus. The institution's Ethics Committee approved the study (No: INT/IEC/2021/SPL-1520, date September 7, 2021). Informed consent was obtained from all patients or their legally authorized representatives in case of the patient's inability to give consent. The study did not receive any external financial support or funding.

Study Definitions

Scrub typhus was diagnosed based on a typical clinical presentation characterized by acute febrile illness with eschar or skin rash, dyspnea, thrombocytopenia, hepatomegaly or splenomegaly, and microbiological confirmation of *Orientia tsutsugamushi* infection. Microbiological confirmation was achieved using enzyme-linked immunosorbent assay (ELISA) for IgM antibodies or polymerase chain reaction (PCR) testing of blood or eschar tissue. For IgM ELISA, the commercially available Scrub Typhus Detect kit (InBios International) was used, which is based on recombinant 56-kD type-specific antigens of the Karp, Kato, Gilliam, and TA716 strains of *Orientia tsutsugamushi*. A cutoff optical density of 0.468 was used to indicate positivity, as recommended by the manufacturer. For PCR, DNA was extracted from blood or eschar tissue using the QIAamp DNA Mini Kit (QIAGEN, Germany). The extracted DNA was then amplified using a primer pair targeting the gene encoding the 56-kDa antigen of the Gilliam strain.

HLH was diagnosed based on the HScore, a validated tool to assess the probability of sHLH in adult patients.[16] The HScore comprises nine parameters (points in the parenthesis): known underlying immunosuppression (18); high temperature: 101.1–102.9°F (33), ≥103°F (49); organomegaly: hepatomegaly or splenomegaly (23), hepatomegaly and splenomegaly (38); number of cytopenia: two lineages (24), three lineages (34); ferritin: 2000–6000 ng/mL (35), >6000 ng/mL (50); triglyceride (TG): 132–354 mg/dL (44), >354 mg/dL (64); fibrinogen ≤2.5 gm/L (30); and aspartate aminotransferase (AST) ≥30 U/L (19); and hemophagocytosis in the bone marrow (35). The score ranges from 0 to 264, with an HScore of ≤100 and ≥241, indicating a probability of sHLH of ≤1 and ≥99%, respectively. We defined HLH as an HScore of 200 or above, corresponding to a probability of 88% or higher for HLH, instead of a widely used cutoff of 169, corresponding to a probability of about 54%.[16] Additionally, we applied the HLH-2004 diagnostic criteria to all patients, which include eight parameters: fever, splenomegaly, cytopenia, high ferritin, high TG or low fibrinogen, hemophagocytosis detected in bone marrow, spleen, or lymph nodes, reduced natural killer cell activity, and elevated soluble interleukin-2 (IL-2) receptor (also soluble CD25). At least 5 of 8 parameters are required to fulfill the criteria.[17]

Patient Evaluation and Management

Upon enrollment, patients underwent a comprehensive evaluation, including detailed history-taking and clinical examination, with particular emphasis on identifying the pathognomonic eschar. Enlargement of the liver and spleen was confirmed using abdominal ultrasonography. Basic laboratory investigations conducted on admission encompassed a complete blood count, serum electrolytes, serum bilirubin, liver enzymes, coagulation profile, fibrinogen, ferritin, TG, blood gas analysis, electrocardiogram, chest radiograph, and abdominal ultrasound. To exclude alternate infectious etiologies, cultures of blood, urine, or other body fluids were performed as appropriate. Additionally, tests for common mimicking tropical acute febrile illnesses such as dengue (NS1 antigen, IgM, and IgG ELISA), malaria (rapid diagnostic kit, malaria antigen, peripheral smear), leptospirosis (IgM ELISA, microagglutination test), and enteric fever (blood culture, Widal test) were conducted. In selected cases, bone marrow aspiration and biopsy were performed to aid in the diagnosis of sHLH, based on the discretion of the treating physician.

The severity of illness was evaluated using baseline prognostic scoring systems, such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) II at admission. Patients were managed according to the standard "Surviving Sepsis Campaign guidelines," using anti-rickettsial antibiotics such as doxycycline and/or azithromycin as the primary treatment.[18] The management of sHLH followed standard guidelines, prioritizing the treatment of scrub typhus.[7] However, in cases with severe or persistent end-organ dysfunction, additional HLH-specific treatments, such as intravenous (IV) steroids or immunoglobulins (IVIG), were initiated at the discretion of the treating physician.[8] The primary outcome measure was in-hospital mortality. Secondary outcome measures included the requirement of intensive organ support during hospitalization, such as invasive mechanical ventilation,

vasopressor therapy, and dialysis treatment, as well as the total duration of hospital stay.

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0, Chicago, IL). Discrete variables were presented as frequency (n) and percentage (%). Continuous variables were described using the mean and standard deviation (SD) or the median and interquartile range (IQR), depending on the normality of the data. Categorical variables were compared using the Chi-square or Fisher's exact test as appropriate, while continuous variables were analyzed using Analysis of Variance (ANOVA) or the Mann–Whitney *U* test, depending on their distribution. The diagnostic accuracy of individual items of the HScore was evaluated by calculating odds ratios (ORs) and 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic utility of various biomarkers, including ferritin, fibrinogen, TG, and C-reactive protein (CRP), in identifying sHLH. This analysis involved calculating the area under the curve (AUC), sensitivity, specificity, false positive and negative rates, likelihood ratios, and diagnostic odds ratios (with 95% CIs). Optimal cutoffs were determined using Youden's index, which maximizes the sum of sensitivity and specificity. The diagnostic performance of various ferritin cutoff values was also thoroughly evaluated. All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

A total of 150 patients with scrub typhus were enrolled. The mean age of patients was 38.8 ± 15.4 years (range 13–75), with a slight female predominance ($n = 81$, 54.0%). Geographically, the majority were from Himachal Pradesh (34.1%), Haryana (27.3%), and Punjab (24.0%), with others from Uttar Pradesh (9.3%), Chandigarh (4.7%), and Jammu and Kashmir (0.7%). Microbiological diagnosis of scrub typhus was achieved with IgM ELISA ($n = 145$, 96.7%), PCR of blood ($n = 37$, 24.7%), or eschar tissue ($n = 12$, 8.0%).

In our study, 28 patients (18.7%) were diagnosed with sHLH. Table 1 presents the baseline clinical characteristics of the study participants. The patients with sHLH had a higher prevalence of high-grade fever, seizures, tachycardia, hepatomegaly, and splenomegaly. Regarding baseline laboratory parameters, no significant differences were observed in hemoglobin, total and differential leucocyte counts, arterial blood gas, serum electrolytes, and renal functions between the groups; however, the sHLH group had marked thrombocytopenia elevated levels of bilirubin, transaminases, and D-dimer (Table 2). Markers of immune hyperactivation or inflammation, such as ferritin, TG, fibrinogen, and CRP, showed significant differences between the two groups (Tables 2 and 3). Figure 1 and Table 4 present the ROC curve analysis evaluating the diagnostic performance of various biomarkers for predicting sHLH. Ferritin demonstrated the highest diagnostic utility. Table 5 details the diagnostic performance of the various cutoff values for ferritin.

In our study, the mean HScore was 150.6 ± 50.3, ranging from 19 to 285, with significantly higher scores observed in the sHLH group (224.9 ± 23.2 vs 133.5 ± 37.8, $p < 0.001$). Notably, 37.3% of patients ($n = 56$) had an HScore of ≥169, the widely used HScore cutoff, suggesting that using the conventional threshold could potentially identify twice as many cases of sHLH. Within the sHLH group, 28.6% of patients (eight patients) also met the HLH-2004 criteria, in contrast to only 4.1% of patients without sHLH (five patients). The average number of HLH-2004 criteria met by the study cohort was 3.1 ± 1.0, which was significantly higher in the sHLH group (4.1 ± 0.8 vs 2.9 ± 1.0, $p < 0.001$).

The patients with sHLH presented with more severe illness at admission compared to those without sHLH, as indicated by higher baseline SOFA and APACHE-II scores (Table 6). The requirement for mechanical ventilation and vasopressor therapy was also higher in the sHLH group. In-hospital mortality was 9.3% ($n = 14$), with a significantly higher rate observed in the sHLH group (21.4 vs 6.6%, $p = 0.025$).

Treatment strategies for sHLH included antimicrobial therapy alone for 18 patients (64.3%) and a combination of immunomodulation and antimicrobials for 10 patients (35.7%). Immunomodulatory therapy included IVIG and steroids in five patients each. IVIG was administered at a dose of 1.6 gm/kg over 3 days in four patients and 0.6 gm/kg for 1 day in one patient. IV steroid therapy included dexamethasone in four patients, started at 10 mg/m^2/day, and hydrocortisone in one patient, initiated at 100 mg thrice a day, which was continued until the resolution of sHLH.

Discussion

In this large prospective study including patients with scrub typhus requiring emergency hospitalization, we found a high prevalence of sHLH at presentation. Patients who presented with high-grade fever, seizures, organomegaly, cytopenia, and significant liver dysfunction were more likely to have sHLH. Regarding various biomarkers, the sHLH group typically had high ferritin, low fibrinogen, high TG, and high CRP, with ferritin showing the highest diagnostic performance in predicting sHLH. Patients with sHLH frequently required mechanical ventilation and vasopressor therapy during hospitalization and had threefold higher in-hospital mortality than those without sHLH.

The spectrum of sHLH varies based on geographic region, demographic factors, the host's immune status, available laboratory facilities, and diagnostic criteria used for HLH.[8] In LMICs like India, endemic infections such as enteric fever, scrub typhus, dengue, malaria, kala-azar, and tuberculosis remain prevalent.[19,20] While the diagnostic criteria for primary HLH in pediatric populations, such as HLH-2004, have been proposed for adult sHLH as well, these may not always be applicable in acute care settings.[7,16,21,22] Investigations like natural killer cell activity, soluble interleukin-2 receptor level, and biopsies for hemophagocytosis may not be readily available or feasible, particularly in LMICs. Therefore, our study used the HScore, a validated tool for adult HLH that incorporates readily accessible laboratory tests and has demonstrated equal or superior diagnostic accuracy to the HLH-2004 criteria, particularly in critically ill patients.[21,22] Moreover, the HScore has been increasingly used to detect sHLH in other tropical infections, such as dengue and malaria, highlighting its utility in diverse clinical scenarios where tropical infections are prevalent and comprehensive diagnostic facilities are limited.[23]

We adopted an HScore cutoff of 200, which is higher than the conventional cutoff of 169 originally described. This decision was based on recent literature indicating that an HScore cutoff of 200 performs comparably to the standard HLH-2004 criteria.[24] Furthermore, considering the overlapping features of scrub typhus and sHLH—such as fever, cytopenia, splenomegaly, hepatomegaly, hepatic dysfunction, and an elevated inflammatory response—we employed a higher HScore cutoff, allowing for more precise identification of sHLH. Our primary objective was to accurately

Table 1: Baseline clinical characteristics of patients with scrub typhus and comparison between patients with and without sHLH

Parameters	*Total (n = 150)*	*sHLH (n = 28)*	*No sHLH (n = 122)*	*p-value*
Age (years), mean ± SD	38.8 ± 15.4	34.0 ± 14.2	39.9 ± 15.4	0.066
Male gender, *n* (%)	69 (46%)	15 (53.6 %)	54 (44.3%)	0.373
Duration of illness (days), mean ± SD	8.2 ± 3.2	8.1 ± 2.7	8.2 ± 3.3	0.788
Fever, *n* (%)	150 (100%)	28 (100%)	122 (100%)	–
Shortness of breath, *n* (%)	132 (88%)	26 (92.9%)	106 (86.9%)	0.528
Abdominal pain, *n* (%)	86 (57.3%)	16 (57.1%)	70 (57.4%)	0.982
Nausea or vomiting, *n* (%)	77 (51.3%)	13 (46.4%)	64 (52.5%)	0.565
Jaundice, *n* (%)	45 (30%)	10 (35.7%)	35 (28.7%)	0.464
Headache, *n* (%)	61 (40.7%)	8 (28.6%)	53 (43.4%)	0.149
Altered sensorium, *n* (%)	49 (32.7%)	12 (42.9%)	37 (30.3%)	0.202
Seizure, *n* (%)	21 (14%)	9 (32.1%)	12 (9.8%)	0.005
Glasgow coma scale, median (IQR)	15 (15–15)	15 (11–15)	15 (15–15)	0.356
Temperature (°F), mean ± SD	101.1 ± 1.6	102.1 ± 1.4	100.8 ± 1.5	<0.001
Pulse rate (/min), mean ± SD	106.9 ± 18.7	114.7 ± 16.8	105.1 ± 18.7	0.015
Mean arterial pressure (mm Hg), mean ± SD	77.8 ± 15.9	73.2 ± 16.4	78.9 ± 15.6	0.092
Respiratory rate (/min), median (IQR)	28 (24–34)	28 (24.5–39)	28 (24–32)	0.189
Eschar, *n* (%)	52 (34.7%)	10 (35.7%)	42 (34.4%)	0.897
Skin rash, *n* (%)	10 (6.7%)	2 (7.1%)	8 (6.6%)	1.000
Lymphadenopathy, *n* (%)	6 (4%)	2 (7.1%)	4 (3.3%)	0.311
Hepatomegaly, *n* (%)	79 (52.7%)	22 (78.6%)	57 (46.7%)	0.002
Splenomegaly, *n* (%)	67 (44.7%)	21 (75%)	46 (37.7%)	<0.001
Lung crackles, *n* (%)	96 (64%)	16 (57.1%)	80 (65.6%)	0.402
Wheeze, *n* (%)	9 (6%)	4 (14.3%)	5 (4.1%)	0.630
Illness severity scores				
APACHE II score, mean ± SD	17.09 ± 5.79	20.21 ± 5.94	16.33 ± 5.51	0.001
SOFA score, mean ± SD	8.42 ± 3.14	10.25 ± 3.03	7.97 ± 3.02	<0.001

APACHE, acute physiology and chronic health evaluation; sHLH, secondary hemophagocytic lymphohistiocytosis; SOFA, sequential organ failure assessment

Table 2: Baseline laboratory parameters of patients with scrub typhus and comparison between patients with and without sHLH

Parameter	*Total (n = 150)*	*sHLH (n = 28)*	*No sHLH (n = 122)*	*p-value*
Hemoglobin (gm/dL), mean ± SD	10.7 ± 1.9	10.8 ± 2.2	10.6 ± 1.9	0.590
Platelet count (per µl), median (IQR)	50,500 (28,750–75,500)	36,000 (16,500–58,500)	53,000 (30,500–83,500)	0.002
Total leucocyte count (per µl), median (IQR)	10,400 (6,900–14,100)	10,100 (5,750–13,900)	10,400 (7,200–14,100)	0.377
Neutrophil (%), mean ± SD	66.0 ± 16.0	68.1 ± 11.0	65.5 ± 17.0	0.442
Lymphocyte (%), mean ± SD	26.5 ± 15.0	23.9 ± 10.7	27.1 ± 15.8	0.307
Monocyte (%), median (IQR)	5 (3.5–7.6)	5.5 (4.2–7.9)	4.9 (3.3–7.4)	0.466
Blood pH, mean ± SD	7.38 ± 0.10	7.38 ± 0.94	7.39 ± 0.10	0.636
PaO_2:FiO_2 ratio, median (IQR)	149 (108–276)	127.5 (99–280.5)	158 (116–270)	0.273
Serum sodium (mEq/L), mean ± SD	135.2 ± 7.2	132.7 ± 6.2	135.9 ± 7.3	0.380
Serum potassium (mEq/L), mean ± SD	4.3 ± 0.7	4.5 ± 0.7	4.3 ± 0.6	0.215
Serum creatinine (mg/dL), median (IQR)	1.4 (0.9–2.3)	1.6 (1.1–2.3)	1.3 (0.8–2.3)	0.218
Total bilirubin (mg/dL), median (IQR)	2.5 (0.9–5.5)	4.55 (1.1–7.6)	2.1 (0.9–5.3)	0.043
Conjugated bilirubin (mg/dL), median (IQR)	1.4 (0.5–3.8)	3.0 (0.4–5.0)	1.3 (0.5–3.3)	0.057
Aspartate transaminase (U/L), median (IQR)	174.5 (119.5–254)	216.5 (160.25–415.5)	167 (101.75–232.5)	0.003
Alanine transaminase (U/L), median (IQR)	92.5 (63–132.5)	117.5 (75.25–168.25)	86 (59.75–128)	0.019

(Contd...)

Table 2: *(Contd...)*

Parameter	*Total (n = 150)*	*sHLH (n = 28)*	*No sHLH (n = 122)*	*p-value*
Alkaline phosphatase (U/L), median (IQR)	257 (165–444)	238.5 (153–429)	257 (166.5–462)	0.767
Serum total protein (gm/dL), mean ± SD	5.4 ± 0.76	5.1 ± 0.53	5.5 ± 0.8	0.055
Serum albumin (gm/dL), mean ± SD	2.4 ± 0.4	2.3 ± 0.3	2.4 ± 0.4	0.327
Prothrombin time (sec), mean ± SD	16.1 ± 3.6	16.9 ± 4.3	15.9 ± 3.4	0.202
Activated partial thromboplastin time (sec), mean ± SD	36.7 ± 9.6	37.9 ± 6.6	36.4 ± 10.1	0.439
D-dimer (ng/mL), median (IQR)	4028.5 (1644.25–9154.5)	7850 (4298.25–15,871.25)	2914.5 (1509–8028)	<0.001
Fibrinogen (gm/L), median (IQR)	1.9 (1.2–2.8)	1.5 (0.8–1.8)	2.2 (1.3–3.0)	<0.001
Triglyceride (mg/dL), median (IQR)	355 (267–458.5)	444.5 (326.25–638.75)	341 (258–432)	0.003
Ferritin (ng/mL), median (IQR)	1641 (728.75–4903.5)	5903.5 (2676.75–21,835)	1263.5 (586.75–3142.25)	<0.001
Ferritin >500 ng/mL, *n* (%)	123 (82%)	28 (100%)	95 (77.9%)	–
C- reactive protein (mg/L), mean ± SD	108.8 ± 81.2	139.8 ± 66.8	101.4 ± 82.8	0.027

PaO_2:FiO_2, the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; sHLH, secondary hemophagocytic lymphohistiocytosis

Table 3: Comparison of individual components of HScore in scrub typhus patients with and without sHLH

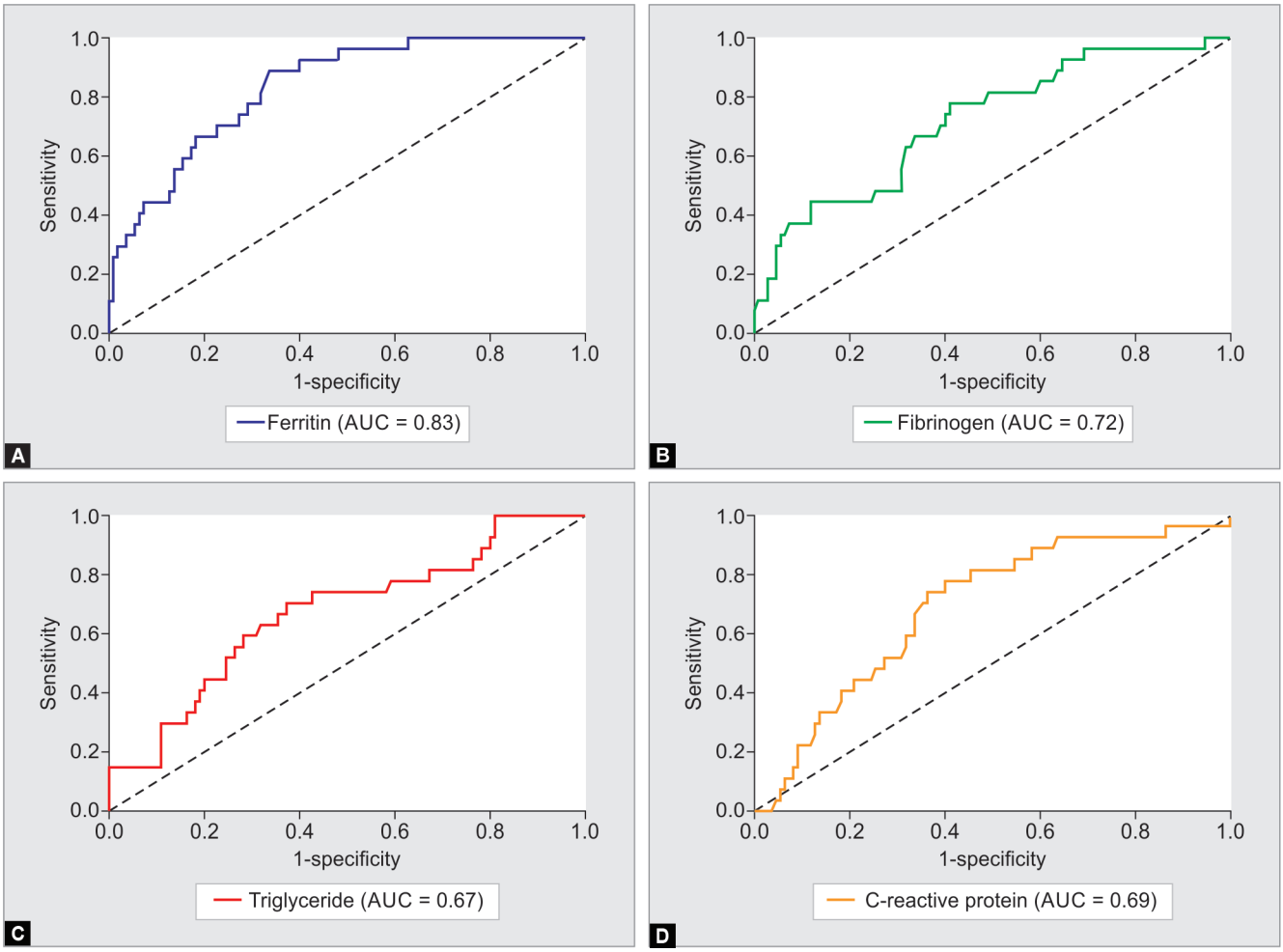
SN	*HScore items*	*sHLH (n = 28)*	*No sHLH (n = 122)*	*Odds ratio*	*p-value*
1.	Immunosuppression	0	0	–	–
2.	Fever				
	101.1–102.9 °F	8 (28.6%)	22 (18.0%)	1.818 (0.710–4.659)	0.209
	≥ 103 °F	11 (39.3%)	18 (14.8%)	3.739 (1.507–9.275)	0.003
3.	Organomegaly				
	Hepatomegaly or splenomegaly	27 (96.4%)	72 (59.0%)	18.750 (2.467–142.519)	<0.001
	Hepatomegaly and splenomegaly	21 (75%)	46 (37.7%)	4.957 (1.955–12.568)	<0.001
4.	Cytopenias[a]				
	Two lineages	12 (42.9%)	25 (20.5%)	2.910 (1.222–6.932)	0.013
	Three lineages	1 (3.6%)	2 (1.6%)	2.222 (0.194–25.406)	0.464
5.	Ferritin (ng/mL)				
	2000–6000	11 (39.3%)	26 (21.3%)	2.389 (0.997–5.723)	0.047
	>6000	14 (50%)	15 (12.3%)	7.133 (2.851–17.845)	<0.001
6.	Triglyceride (mg/dL)				
	132–354	7 (25%)	59 (48.4%)	0.356 (0.141–0.899)	0.025
	> 354	21 (75%)	52 (42.6%)	4.038 (1.597–10.211)	0.002
7.	Fibrinogen ≤ 2.5 gm/L	24 (85.7%)	73 (59.8%)	4.027 (1.316–12.327)	0.010
8.	Aspartate transaminase ≥ 30 U/L	28 (100%)	118 (96.7%)	–	–
9.	Hemophagocytosis in bone marrow, *n* (%)	7/7 (100%)	0/0	–	–

Cytopenias[a] are defined as hemoglobin ≤9.2 gm/dL and/or total leucocyte count ≤5,000/mm^3 and/or platelets ≤110,000/mm^3. sHLH, secondary hemophagocytic lymphohistiocytosis

identify the subset of scrub typhus patients with sHLH who could benefit from immunomodulatory therapy in addition to antimicrobial agents. The use of a conventional cutoff of 169 would have resulted in the diagnosis of sHLH in over one-third of our study population, significantly inflating the number of cases.

All patients with scrub typhus presented with fever; however, high-grade fever at presentation was more indicative of sHLH. Similarly, while thrombocytopenia and liver-test abnormalities were commonly observed at baseline, marked thrombocytopenia, cytopenia involving two or more lineages, significant transaminitis, and hyperbilirubinemia were strong predictors of sHLH. Consistent with previous studies, liver dysfunction and organomegaly (hepatomegaly or splenomegaly) were notable findings in the sHLH group, making their absence a strong indicator against the diagnosis of sHLH.[7–12] Furthermore, studies have suggested that liver injury, a poor prognostic marker in scrub typhus, may often result from unrecognized underlying sHLH, contributing to significant liver dysfunction.[3,25]

The central nervous system (CNS) involvement can vary widely in cases of scrub typhus and adult sHLH.[3,7,8] In our study, seizures at presentation were particularly indicative of sHLH, despite similarity of other CNS features such as altered mental status, headaches, and Glasgow coma scale in both patient groups. The immediate diagnosis of sHLH in patients presenting with CNS complications is crucial due to the associated poor prognosis, underscoring the need for a lower threshold in initiating immunosuppressive therapy.[7,8] Conversely, pulmonary, renal, and metabolic parameters did not show significant differences between the two groups.



Figs 1A to D: Receiver operating characteristic (ROC) curves demonstrating the diagnostic utility of various biomarkers in predicting secondary hemophagocytic lymphohistiocytosis in patients with scrub typhus. Panels: (A) Ferritin (AUC = 0.83); (B) Fibrinogen (AUC = 0.72); (C) Triglyceride (AUC = 0.67); (D) C-reactive protein (AUC = 0.69). AUC, Area under the curve

Table 4: The diagnostic performance of the various biomarkers for scrub typhus-associated hemophagocytic lymphohistiocytosis

Parameters	*Ferritin*	*Fibrinogen*	*Triglyceride*	*C-reactive protein*
Area under curve	0.83 (0.76–0.91)	0.72 (0.61–0.82)	0.67 (0.56–0.79)	0.69 (0.58–0.79)
Optimal cutoff	2000 ng/mL	1.84 gm/L	378 mg/dL	99 mg/L
Sensitivity	89.29% (71.77–97.73)	78.57% (59.05–91.70)	71.43% (51.33–86.78)	77.78% (57.74–91.38)
Specificity	66.39% (57.28–74.69)	57.63% (48.19–66.67)	64.10% (54.71–72.76)	58.77% (49.17–67.91)
False negative rate	10.71% (2.27–28.23)	21.43% (8.30–40.95)	28.57% (13.22–48.67)	22.22% (8.62–42.26)
False positive rate	33.61% (25.31–42.72)	42.37% (33.33–51.81)	35.90% (27.24–45.29)	41.23% (32.09–50.83)
Positive likelihood ratio	2.66 (2.01–3.52)	1.85 (1.39–2.47)	1.99 (1.42–2.79)	1.89 (1.40–2.54)
Negative likelihood ratio	0.16 (0.12–0.25)	0.37 (0.12–0.85)	0.45 (0.18–0.89)	0.38 (0.13–0.86)
Diagnostic odds ratio	16.46 (4.69–57.76)	4.99 (1.8833–13.20)	4.46 (1.81–11.01)	4.99 (1.87–13.31)
Youden's index	0.557 (0.415–0.699)	0.362 (0.186–0.538)	0.355 (0.167–0.544)	0.365 (0.184–0.546)

Values are given in percentage (95% CI) or ratio (95% CI)

Overall, cases of sHLH were characterized by greater illness severity and more pronounced organ dysfunction at presentation, as evidenced by higher APACHE-II and SOFA scores. Although a late clinical presentation is associated with an increased incidence of sHLH in children with scrub typhus, the duration of symptoms did not predict sHLH in our adult cohort, indicating that sHLH can complicate scrub typhus at any stage of the illness.[26]

Ferritin has been validated as a crucial diagnostic biomarker for both primary and sHLH. Our study reinforces its utility in identifying sHLH triggered by scrub typhus, confirming the widely

Table 5: The diagnostic performance of the various cutoff values of the serum ferritin (ng/mL) for scrub typhus-associated hemophagocytic lymphohistiocytosis

Parameters	*1,000*	*2,000*	*6,000*	*10,000*
Sensitivity	100%	89.29% (71.77–97.73)	50.00% (30.65–69.35)	39.29% (21.50–59.42)
Specificity	39.34% (30.62–48.49)	66.39% (57.28–74.69)	87.70% (80.53–92.95)	94.26% (88.54–92.95)
False negative rate	0%	10.71% (2.27–28.23)	50.00% (30.65–69.35)	60.71% (40.58–78.50)
False positive rate	60.66% (51.41–69.39)	33.61% (25.31–42.72)	12.30% (7.05–19.47)	5.74% (2.34–11.46)
Positive likelihood ratio	1.65 (1.43–1.90)	2.66 (2.01–3.52)	4.07 (2.23–7.42)	6.85 (2.91–16.08)
Negative likelihood ratio	0	0.16 (0.12–0.25)	0.57 (0.43–0.75)	0.64 (0.52–0.80)
Diagnostic odds ratio	–	16.46 (4.69–57.76)	1.13 (2.85–17.84)	10.62 (3.62–31.17)
Youden's index	0.393 (0.307–0.480)	0.557 (0.415–0.699)	0.377 (0.183–0.571)	0.335 (0.150–0.521)

Values are given in percentage (95% CIs) or ratio (95% CIs)

Table 6: Outcomes of patients with scrub typhus and comparison between patients with and without sHLH

Parameters	*Total (n = 150)*	*sHLH (n = 28)*	*No sHLH (n = 122)*	*p-value*
Mortality rate, *n* (%)	14 (9.3%)	6 (21.4%)	8 (6.6%)	0.025
Mechanical ventilation requirement, *n* (%)	53 (35.3%)	18 (64.3%)	35 (28.7%)	<0.001
Duration of mechanical ventilation (days), median (IQR)	5 (2–6)	4 (2–7.5)	5 (2.5–6)	0.671
Vasopressor requirement, *n* (%)	58 (38.7%)	17 (60.7%)	41 (33.6%)	0.008
Renal replacement therapy, *n* (%)	12 (8%)	2 (7.1%)	10 (8.2%)	1.000
Hospital stay (days), median (IQR)	7 (5–9)	7.5 (4–11)	7 (5–9)	0.541

sHLH, secondary hemophagocytic lymphohistiocytosis

recognized cutoff of 2000 ng/mL as optimal.[7,16] In our cohort, this threshold demonstrated a sensitivity of 90% and a specificity of 66%, providing equal or superior diagnostic accuracy compared to primary HLH or virus-associated sHLH.[27] A baseline ferritin level of ≥2000 ng/mL should prompt consideration of sHLH, while levels below 1000 ng/mL effectively exclude sHLH in scrub typhus. Although retrospective studies involving heterogeneous disorders have suggested higher than the current cutoffs for diagnosing HLH, these findings may not directly apply to a specific disorder like scrub typhus.[28,29] Furthermore, higher thresholds, such as 6,000 and 10,000 ng/mL, increase specificity (88% and 95%, respectively) and maintain moderate sensitivity (50 and 40%, respectively), establishing them as particularly strong predictors of sHLH in this infection.

In our study, low fibrinogen levels showed a modest diagnostic utility for sHLH. Hypofibrinogenemia in sHLH typically results from increased consumption due to hyperactivation of the coagulation system or disseminated intravascular coagulation, often triggered by severe systemic inflammation.[30] Correspondingly, this extensive coagulation activity also results in significantly elevated d-dimer levels, the fibrin degradation products, in our sHLH cases.[30]

Elevated TG levels are common in HLH, reflecting its hyperinflammatory state. Although elevated TGs receive higher points than other items in the original HScore, our study found that TG had the least diagnostic utility compared to other biomarkers. The optimal cutoff for TG was calculated to be 378 mg/dL, significantly higher than the 132 mg/dL threshold used in the HScore. A possible explanation is the frequent occurrence of liver dysfunction in scrub typhus, which impairs TG clearance. This, along with increased lipolysis due to the cytokine storm, typically contributes to elevated TG levels in HLH.[31] In our cohort, HScore items—TG levels between 132 and 354 mg/dL and AST >30 U/L—did not predict sHLH in scrub typhus. These results suggest that higher values of TG and AST are necessary for identifying HLH in scrub typhus.

In our study, we evaluated CRP, a widely available inflammatory marker, for its potential as a predictive marker for sHLH in scrub typhus, especially in resource-limited settings of LMICs. However, it demonstrated lower diagnostic utility compared to ferritin and fibrinogen. Our findings align with previous reports, suggesting that while high CRP can signal systemic inflammation, it lacks the specificity and sensitivity required to effectively identify sHLH.[32]

Bone marrow examinations were performed in only seven cases, decided at the discretion of the treating clinician. While more frequent use might have improved the HScore points for some patients, the invasiveness and practical challenges limit its routine use. Despite its name, the presence of hemophagocytosis is not synonymous with HLH, as it can also occur in conditions of systemic inflammation such as sepsis, following blood transfusions, or during the postoperative period.[22,33] Additionally, hemophagocytosis often varies in sensitivity and may not be present in the early stages of the disease.[33–35] Moreover, studies have indicated that omitting hemophagocytosis from diagnostic criteria of HScore or HLH-2004 only marginally reduces the accuracy of HLH diagnosis compared to the full criteria.[22,36]

Our study highlights the severe clinical complexities and adverse outcomes associated with sHLH in patients with scrub typhus. Consistent with the previous studies, sHLH cases required significantly more mechanical ventilation and vasopressor support, and the in-hospital mortality rate was markedly higher compared to patients without sHLH.[8,9,37] These findings emphasize the critical

need for early identification of sHLH, enabling timely and intensive care, along with tailored, aggressive management strategies.

Given the heterogeneity of sHLH in adults, treatment must be individualized, focusing on controlling hyperinflammation and addressing primary disease triggers.[7,38] While many infection-associated HLH cases resolve with targeted antimicrobial therapy, the initiation of specific HLH treatments like IVIG or dexamethasone should be based on careful clinical judgment and assessment of organ function.[7,38] In our cohort, only one-third of the patients with sHLH received IVIG or steroids. The challenges of using such treatments in LMICs, compounded by a hesitancy to administer steroids during infections and the high costs of IVIG, highlight the urgent need for further research into the specific guidance for the choice, timing, and duration of immunomodulatory therapy in infection-associated sHLH.[20]

Limitation

Our study has several limitations. First, being conducted at the emergency medicine unit of a single apex-care hospital, our findings may not be generalizable to all patients with scrub typhus. The observed high prevalence of sHLH could be attributed to the severe cases of scrub typhus. Second, the biomarkers, i.e., ferritin, fibrinogen, TG, and CRP, were available only on weekdays. As a result, these tests could not be immediately performed for patients admitted over the weekend, from Saturday afternoon to Monday morning. This limitation might have delayed the timely diagnosis of sHLH. Third, HLH-directed treatments were prescribed based on the treating physicians' clinical judgment regarding their initiation, choice, timing, and duration. This variability prevents us from definitively assessing the efficacy of specific HLH-directed therapies. Fourth, due to its non-availability, the soluble IL-2 receptor, a strong predictor of HLH, could not be evaluated and compared with other biomarkers in our study.

Conclusion

This study underscores the critical importance of early detection and tailored treatment in managing scrub typhus-associated sHLH, a severe complication frequently observed in patients requiring emergency hospitalization. Patients with sHLH typically present with multi-organ failure, often require intensive organ support, and carry significantly high mortality. Serum ferritin emerged as the most valuable biomarker, effectively distinguishing sHLH with high sensitivity and specificity. The variability observed in HLH-directed treatment approaches highlights the urgent need for standardized protocols to ensure effective and consistent care, thereby improving patient outcomes.

Acknowledgment

The authors would like to thank Mrs Sunaina Verma for her help in statistical analysis.

Orcid

Suresh Selvam https://orcid.org/0000-0002-2195-1089
Akshit Tuli https://orcid.org/0009-0008-3563-5563
Kumar P Yuvasai https://orcid.org/0009-0007-7622-3496
Shashikant Saini https://orcid.org/0000-0003-1398-4793
Sathvik R Erla https://orcid.org/0009-0000-6715-1709
Jyotdeep Kaur https://orcid.org/0000-0003-0284-4517
Manisha Biswal https://orcid.org/0000-0003-2016-3678
Navneet Sharma https://orcid.org/0000-0001-5707-9686
Ashok K Pannu https://orcid.org/0000-0002-4476-3478

References

1. Dasgupta S, Asish PR, Rachel G, Bagepally BS, Chethrapilly Purushothaman GK. Global seroprevalence of scrub typhus: A systematic review and meta-analysis. Sci Rep 2024;14(1):10895. DOI: 10.1038/s41598-024-61555-9.
2. Peng PY, Duan HY, Xu L, Zhang LT, Sun JQ, Zu Y, et al. Epidemiologic changes of a longitudinal surveillance study spanning 51 years of scrub typhus in mainland China. Sci Rep 2024;14(1):3138. DOI: 10.1038/s41598-024-53800-y.
3. Pannu AK, Saroch A, Sharda SC, Debnath MK, Biswal M, Sharma N, et al. Circulatory and hepatic failure at admission predicts mortality of severe scrub typhus patients: A prospective cohort study. Asian Pac J Trop Med 2021;14(5):209–213. DOI: 10.4103/1995-7645.314113.
4. Varghese GM, Dayanand D, Gunasekaran K, Kundu D, Wyawahare M, Sharma N, et al. INTREST Trial Investigators. Intravenous doxycycline, azithromycin, or both for severe scrub typhus. N Engl J Med 2023;388(9):792–803. DOI: 10.1056/NEJMoa2208449.
5. Pannu AK, Debnath MK, Sharma N, Biswal M, Vijayvergia R, Bhalla A, et al. Circulating cardiac biomarkers and echocardiographic abnormalities in patients with scrub typhus: A prospective cohort study from a tertiary care center in North India. J Vector Borne Dis 2021;58(3):193–198. DOI: 10.4103/0972-9062.321754.
6. Pannu AK, Smitha S, Ravi N, Chander Y, Biswal M, Suri V, et al. Scrub typhus cholecystitis. J Vector Borne Dis 2020;57(4):375–377. DOI: 10.4103/0972-9062.313960.
7. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133(23):2465–2477. DOI: 10.1182/blood.2018894618.
8. Campo M, Berliner N. Hemophagocytic lymphohistiocytosis in adults. Hematol Oncol Clin North Am 2015;29(5):915–925. DOI: 10.1016/j.hoc.2015.06.009.
9. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. Hematology Am Soc Hematol Educ Program 2015;2015(1):177–182. DOI: 10.1182/asheducation-2015.1.177.
10. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. Blood Res 2021;56(S1):S17–S25. DOI: 10.5045/br.2021.2020323.
11. Janka GE, Lehmberg K. Hemophagocytic syndromes–an update. Blood Rev 2014;28(4):135–142. DOI: 10.1016/j.blre.2014.03.002.
12. Pannu AK, Singla V, Suri V, Kumar R, Mathur Y, Mohindra R, et al. Adult-onset Still's disease and fever of unknown origin in India. Clin Exp Med 2023;23(5):1659–1666. DOI: 10.1007/s10238-022-00903-3.
13. Naoi T, Morita M, Kawakami T, Fujimoto S. Hemophagocytic lymphohistiocytosis associated with scrub typhus: Systematic review and comparison between pediatric and adult cases. Trop Med Infect Dis 2018;3(1):19. DOI: 10.3390/tropicalmed3010019.
14. Pannu AK, Sharma N. Tropical infection induced hemophagocytic lympho-histiocytosis. Int J Blood Res Disord 2016;1(1):1–4. DOI: 10.15226/2639-7986/1/1/00101.
15. Grangé S, Buchonnet G, Besnier E, Artaud-Macari E, Beduneau G, Carpentier D, et al. The Use of Ferritin to Identify Critically Ill Patients with Secondary Hemophagocytic Lymphohistiocytosis. Crit Care Med 2016;44(11):e1045–e1053. DOI: 10.1097/CCM.0000000000001878.
16. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014;66(9):2613–2620. DOI: 10.1002/art.38690.
17. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for

hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(2):124–131. DOI: 10.1002/pbc.21039.
18. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–1247. DOI: 10.1007/s00134-021-06506-y.
19. Fazal F, Gupta N, Soneja M, Mitra DK, Satpathy G, Panda SK, et al. Clinical profile, treatment, and outcome of patients with secondary hemophagocytic lymphohistiocytosis in critically ill patients: A prospective observational study. Indian J Crit Care Med 2022;26(5):564–567. DOI: 10.5005/jp-journals-10071-24136.
20. Pannu AK, Bhalla A. Secondary Hemophagocytic lymphohistiocytosis: Think of the devil lurking! Indian J Crit Care Med 2022;26(5):545–546. DOI: 10.5005/jp-journals-10071-24216.
21. Knaak C, Nyvlt P, Schuster FS, Spies C, Heeren P, Schenk T, et al. Hemophagocytic lymphohistiocytosis in critically ill patients: Diagnostic reliability of HLH-2004 criteria and HScore. Crit Care 2020;24(1):1–9. DOI: 10.1186/s13054-020-02941-3.
22. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, et al. Performances of the H-Score for diagnosis of hemophagocytic lymphohistiocytosis in adult and pediatric patients. Am J Clin Pathol 2016;145(6):862–870. DOI: 10.1093/ajcp/aqw076.
23. Kan FK, Tan CC, Von Bahr Greenwood T, Khalid KE, Supramaniam P, Hed Myrberg I, et al. Dengue infection complicated by hemophagocytic lymphohistiocytosis: Experiences from 180 patients with severe dengue. Clin Infect Dis 2020;70(11):2247–2255. DOI: 10.1093/cid/ciz499.
24. Bilston L, Croden J, Taparia M, Karkhaneh M, Grossman J, Sun HL. Validation of the HScore and the HLH-2004 diagnostic criteria for the diagnosis of hemophagocytic lymphohistiocytosis in a multicenter cohort. Eur J Haematol 2022;109(2):129–137. DOI: 10.1111/ejh.13779.
25. Diamond T, Bennett AD, Behrens EM. The liver in hemophagocytic lymphohistiocytosis: Not an innocent bystander. J Pediatr Gastroenterol Nutr 2023;77(2):153–159. DOI: 10.1097/MPG.0000000000003807.
26. Basu A, Chowdhoury SR, Sarkar M, Khemka A, Mondal R, Datta K, et al. Scrub typhus-associated hemophagocytic lymphohistiocytosis: Not a rare entity in pediatric age group. J Trop Pediatr 2021;67(1):fmab001. DOI: 10.1093/tropej/fmab001.
27. Lehmberg K, McClain KL, Janka GE, Allen CE. Determination of an appropriate cut-off value for ferritin in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2014;61(11):2101–2103. DOI: 10.1002/pbc.25058.
28. Otrock ZK, Hock KG, Riley SB, de Witte T, Eby CS, Scott MG. Elevated serum ferritin is not specific for hemophagocytic lymphohistiocytosis. Ann Hematol 2017;96(10):1667–1672. DOI: 10.1007/s00277-017-3072-0.
29. Saeed H, Woods RR, Lester J, Herzig R, Gul Z, Monohan G. Evaluating the optimal serum ferritin level to identify hemophagocytic lymphohistiocytosis in the critical care setting. Int J Hematol 2015;102(2):195–199. DOI: 10.1007/s12185-015-1813-1.
30. Luo X, Zhou C, Ji C, Lu C, Luo Y, Chen Z, et al. Hypofibrinogenemia is an independent predictor of hemophagocytic lymphohistiocytosis in children with sepsis. Sci Rep 2023;13(1):17936. DOI: 10.1038/s41598-023-44628-z.
31. Cheng W, Wang L, Gao X, Duan L, Shu Y, Qiu H. Prognostic value of lipid profile in adult hemophagocytic lymphohistiocytosis. Front Oncol 2023;13:1083088. DOI: 10.3389/fonc.2023.1083088.
32. Lehmberg K, Pink I, Eulenburg C, Beutel K, Maul-Pavicic A, Janka G. Differentiating macrophage activation syndrome in systemic juvenile idiopathic arthritis from other forms of hemophagocytic lymphohistiocytosis. J Pediatr 2013;162(6):1245–1251. DOI: 10.1016/j.jpeds.2012.11.081.
33. Suster S, Hilsenbeck S, Rywlin AM. Reactive histiocytic hyperplasia with hemophagocytosis in hematopoietic organs: A reevaluation of the benign hemophagocytic proliferations. Hum Pathol 1988;19(6):705–712. DOI: 10.1016/S0046-8177(88)80177-1.
34. Gupta A, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008;50(2):192–194. DOI: 10.1002/pbc.21441.
35. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Hematology Am Soc Hematol Educ Program 2009;2009(1):127–131. DOI: 10.1182/asheducation-2009.1.127.
36. Nyvlt P, Schuster FS, Ihlow J, Heeren P, Spies C, Hiesgen J, et al. Value of hemophagocytosis in the diagnosis of hemophagocytic lymphohistiocytosis in critically ill patients. Eur J Haematol 2024;112(6):917–926. DOI: 10.1111/ejh.14185.
37. Knaak C, Schuster FS, Spies C, Vorderwülbecke G, Nyvlt P, Schenk T, et al. Hemophagocytic lymphohistiocytosis in critically ill patients. Shock 2020;53(6):701–709. DOI: 10.1097/SHK.0000000000001454.
38. La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Program 2015;2015(1):190–196. DOI: 10.1182/asheducation-2015.1.190.