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# Clinical Characteristics and Outcomes of Pediatric Hemophagocytic Lymphohistocytosis: A Retrospective Study from a Tertiary Center in Jordan

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**ABSTRACT**

**Background:** Hemophagocytic lymphohistiocytosis (HLH) is a rare but severe hyperinflammatory syndrome caused by uncontrolled activation of macrophages and cytotoxic T cells. It is frequently underdiagnosed, leading to significant morbidity and mortality in pediatric populations. Early identification and treatment are critical to improving prognosis.

**Materials and Methods:** This retrospective study analyzed demographic, clinical, and laboratory data of pediatric patients aged 0 to 18 years diagnosed with HLH according to the HLH-2004 criteria. Patients admitted to our center between February 2021 and February 2023 were included. We aimed to describe common presenting symptoms, laboratory abnormalities , treatment modalities, and patient outcomes.

**Results:** A total of 35 children diagnosed with HLH were included; 51% were female. The mean age was 6.1 years, with an age range from birth to 18 years. Fever was the most frequent presenting symptom, reported in 85% of cases. Hemophagocytosis in bone marrow aspirates was detected in 41% of patients. The overall mortality rate was 11%. Notably, 20% of patients tested positive for anti-COVID-19 IgG antibodies, suggesting a possible temporal association with the development of HLH, Comparative analysis indicated that deceased patients had significantly lower fibrinogen levels ($p = 0.04$) and higher triglyceride levels ($p = 0.03$). Treatment regimens varied according to clinical presentation and severity.

**Conclusion:** HLH remains a challenging diagnosis due to its variable presentation and potential to rapidly progress to life-threatening immune activation. Prompt recognition and timely initiation of appropriate therapy are vital for improving outcomes in affected children. Increased awareness among clinicians and early intervention can reduce morbidity and mortality associated with this condition.

**Keywords:** Cytokine Syndrome; Fever; Hemophagocytic lymphohistiocytosis (HLH); Hypertriglyceridemia; Hypofibrinogenemia; Inflammatory Process; Pancytopenia

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by hyperinflammation and immune dysregulation in both adults and children. This condition often results in multiorgan failure, malignancy, and death[1,2]. Clinically, HLH manifests as persistent high-grade fever, hepatomegaly, and lymphadenopathy. Laboratory findings frequently include pancytopenia, elevated liver enzymes,

hypertriglyceridemia, increased levels of interleukin-6 (IL-6), interferon-alpha (IFN-α), and tumor necrosis factor (TNF) [3–5]. Histopathological evaluation of bone marrow or reticuloendothelial tissues reveals engulfed hematopoietic cells by activated macrophages [6,7].

HLH was first described in 1939 and initially thought to be a variant of Hodgkin's disease due to similarities in clinical and laboratory features[8]. According to the HLH-2004 diagnostic guidelines, splenomegaly is among the key criteria, along with fever ≥38.5°C, cytopenias, hypertriglyceridemia, presence of hemophagocytosis in bone marrow, decreased natural killer (NK) cell activity, elevated soluble IL-2 receptor levels, and hyperferritinemia (ferritin ≥500 μg/L) [27].

HLH exists in two forms: primary (familial) and secondary[9]. Primary HLH is a genetically inherited condition typically presenting in infancy and is caused by mutations affecting the function of cytotoxic CD8+ T cells and NK cells, leading to uncontrolled cytokine production and macrophage activation[10,11]. In contrast, secondary HLH is triggered by external factors such as infections, autoimmune diseases, or malignancies[12].

Accurately estimating HLH prevalence remains challenging due to overlapping symptoms with other conditions and variability in diagnostic criteria[1,13]. Population-based studies are limited. In Sweden, the incidence of primary HLH is estimated at 0.12–0.15 per 100,000 live births per year[14]. Reported mortality rates vary, with 16% for primary HLH in China (2013–2018) and 39% for secondary HLH in the United States (2007–2017) [15,16].

The HLH-94 international study marked a significant milestone in HLH management by integrating chemotherapy, immunotherapy, and bone marrow transplantation, resulting in improved 3-year survival rates of up to 62% for familial or recurrent disease [17,18].

Despite global progress in HLH diagnosis and treatment, data regarding the prevalence, clinical characteristics, and outcomes of HLH in the Middle East, including Jordan, remain limited. Therefore, in this retrospective, observational study conducted at a single tertiary center in Jordan, we aim to describe a pediatric HLH cohort and evaluate the clinical and laboratory characteristics associated with the disease.

## MATERIALS AND METHODS

### Study Design

This retrospective observational study was conducted at King Abdullah University Hospital (KAUH), a single tertiary care center in Jordan. Pediatric patients diagnosed with hemophagocytic lymphohistiocytosis (HLH) between February 2021 and February 2023 were included. Ethical approval was obtained from the Institutional Review Board (IRB) at Jordan University of Science and Technology in February 2023. The study adhered to the principles of the Declaration of Helsinki (1975). Informed consent was waived by the IRB due to the retrospective nature of the study, as obtaining consent was impractical and the research posed no more than minimal risk to patients. All patient data were anonymized to ensure confidentiality and privacy.

### Data Collection

A total of 35 pediatric patients diagnosed with HLH over the two-year study period were included, reflecting the rarity of the disease and the limited annual case load at our institution.

Patients were included if they fulfilled at least five of the eight diagnostic criteria for hemophagocytic lymphohistiocytosis according to the HLH-2004 guidelines.

Data were retrospectively collected from electronic medical records and included demographic variables (age, gender), clinical features (e.g., hepatomegaly, splenomegaly), and laboratory investigations. Laboratory parameters included white blood cell count (WBC), hemoglobin (Hb), platelets, neutrophils, D-dimer, triglycerides, fibrinogen, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin.

Natural killer (NK) cell cytotoxicity and soluble interleukin-2 receptor (sCD25) assays were not available at our center during the study period and were therefore not performed.

Genetic testing was selectively conducted in patients with clinical suspicion of familial HLH or a relevant

family history. Only two patients underwent genetic analysis, both of whom were confirmed to have primary HLH. Limitations in testing availability and resource constraints, including the lack of whole-exome sequencing, restricted broader genetic screening.

Bone marrow aspiration was performed in 27 of the 35 patients. The procedure was indicated when clinical and laboratory features were suggestive of HLH and served to support the diagnosis rather than act as a sole diagnostic criterion.

Potential HLH triggers were investigated through clinical evaluation, microbiological testing, imaging, and detailed review of patient history. These included infectious etiologies (viral and bacterial), autoimmune diseases, malignancies, and recent COVID-19 infection. Viral infections were confirmed using polymerase chain reaction (PCR) and serological assays when available.

**Statistical analysis**

Continuous variables were summarized as means, while categorical variables were presented as frequencies and percentages. The Wilcoxon rank-sum test (Mann–Whitney U test) was used to evaluate associations involving continuous variables. For categorical variables with expected frequencies below five, the Chi-square ($\chi^2$) test or Fisher's exact test was applied as appropriate. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.2.3; Vienna, Austria)

## RESULTS

**Demographics and Clinical Features**

A total of 35 pediatric patients diagnosed with HLH were included in the study. The cohort consisted of 18 females (51%) and 17 males (49%), with ages ranging from birth to 18 years and a mean age of 6.1 months. Among these, two patients (6%) were confirmed to have familial HLH through genetic testing, while the remaining 33 cases (94%) were classified as secondary HLH.

Fever was the most commonly reported symptom, observed in 85% of patients. Other clinical manifestations included pallor (23%), skin rash (20%), vomiting (9%), and respiratory symptoms (29%). None of the patients exhibited neurological or renal involvement. Bone marrow aspiration was performed in 27 patients; hemophagocytosis was identified in 11 (41%).

Both hepatomegaly and splenomegaly were present in 31% of the cases. Table 1 presents the demographic and clinical features of the study population.

**Table 1:** Baseline characteristics of included HLH patients

| Characteristics | N =35 |
|---|---|
| Age (years), Range | (0-18) |
| Sex, n (%) | |
| Female | 18 (51%) |
| Male | 17(49%) |
| Fever, n (%) | 30(85%) |
| Skin rash, n (%) | 7 (20%) |
| Pallor, n (%) | 8 (23%) |
| Vomiting, n (%) | 3 (9 %) |
| Respiratory symptoms, n (%) | 10 (29%) |
| Neurological symptoms, n (%) | |
| No | 35(100%) |
| Renal failure, n (%) | |
| No | 35(100%) |
| Hemophagocytosis in BM, n (%) | 11/27 (41%) |
| Hepatomegaly, splenomegaly n (%) | 11(31%) |

Values are presented as number of patients (n) and percentage (%). Percentages are calculated based on available data.

**Identified Triggers**

Potential HLH triggers were identified in a subset of patients. Viral infections accounted for 14% of cases, autoimmune diseases for 6%, and malignancies for another 6%. In the majority of patients (74%), no specific trigger could be identified. Epstein–Barr virus (EBV) was the most frequently detected viral cause, followed by cytomegalovirus (CMV)

Some patients developed HLH after a documented or suspected previous COVID-19 infection ; 20% of the patients tested positive for anti-COVID-19 IgG antibodies, suggesting prior infection, and 17 others reported close contact with confirmed COVID-19 cases but tested negative. This suggests a potential temporal association.

**Laboratory Parameters**

Laboratory results are summarized in Table 2. The mean white blood cell (WBC) count was 9.0 ×10^ 9/L (range: 1.5–37), hemoglobin averaged 9.92 g/dL

(range: 6–18), and platelet count averaged 205 $\times 10^3/mm^3$ (range: 10–780). Neutrophil percentage ranged from 12% to 83% with a mean of 45%.

Skewed laboratory parameters were presented as median and interquartile range (IQR). The median ferritin level was 1407 ng/mL (IQR 437–2409.5) , median fibrinogen was 183.5 mg/dL (IQR 130–300) , median D-dimer was 4.0 (IQR 1.7–9.8) , median LDH was 1364.5 U/L (IQR 930–4500) , median CRP was 22 mg/L (IQR 4.5–47.5), median triglyceride level was 2.75 mmol/L (IQR 1.45–4.0) , and the median ESR was 22 mm/hr (IQR 12–50)

**Table 2:** Laboratory findings among pediatric HLH patients (N =35)

| Variables | Value/unit |
|---|---|
| WBC ,mean | 9 (*10^ 9/L) |
| HB, mean | 9.92 (g/dl) |
| Platelets ,mean | 205 (*10 ^ 3/mm3) |
| Neutrophils ,mean | 45% |
| D dimer ,median | 4 |
| LDH ,median | 1364.5 (U/L) |
| CRP , median | 22 (mg/L) |
| ESR , median | 22 (mm/hr) |
| Fibrinogen,median | 183.5 (mg/dl) |
| Ferritin, median | 1407 (ng/ml) |
| Triglyceride,median | 2.75 (mmol/L) |

Values presented as mean/median. Units included for clarity.
Abbreviations: WBC: White blood cells, HB: Hemoglobin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate

## Frequency of Laboratory Abnormalities

Table 3 outlines the prevalence of abnormal laboratory parameters. Hyperferritinemia (>500 ng/mL) was observed in 85% of patients, while 54% had low fibrinogen (<150 mg/dL), and 48% showed elevated D-dimer levels. Hypertriglyceridemia (>3 mmol/L) was found in 37% of cases, elevated liver enzymes in 63%, and hypoalbuminemia in 43%. Leukopenia ($<4.5\times10^3/mm^3$) and thrombocytopenia ($<100\times10^3/mm^3$) were noted in 70% of patients, LDH >1,000 U/L in 51%, and anemia in 60%.

**Table 3:** Laboratory Abnormalities Observed in Pediatric HLH Patients (N = 35)

| Laboratory parameter | Cut-off / Category | N (%) |
|---|---|---|
| Lactate dehydrogenase (LDH, IU/L) | >5,000 | 6 (17%) |
| | >1,000 | 18 (51%) |
| D-dimer | Positive | 17 (48%) |
| | Negative | 18 (51%) |
| Triglycerides (mmol/L) | >4 | 6 (17%) |
| | >3 | 13 (37%) |
| Fibrinogen (mg/dL) | <150 | 19 (54%) |
| | >250 | 9 (25%) |
| Ferritin (ng/mL) | >10,000 | 2 (5%) |
| | >500 | 25 (70%) |
| White blood cells (×10^ 9/L) | <4.5 | 25 (71%) |
| Platelets ($\times10^3/mm^3$) | <100 | 25 (70%) |
| | <20 | 2 (6%) |
| Hemoglobin (Hb, g/dL) | <9 | 21 (60%) |
| | <7 | 7 (20%) |
| Elevated liver enzymes (ALT, AST) | Yes | 22 (63%) |

Values are presented as number of patients (n) and percentage (%).

**ICU Admission and Mortality**

Six patients (17%) required admission to the intensive care unit (ICU). Among them, two required invasive mechanical ventilation. The overall mortality rate was 11% (n=4), with deceased patients having a mean age of 17 months. Two of the deceased had genetically confirmed primary HLH. All deceased patients had hyperferritinemia and hypertriglyceridemia, while three had low fibrinogen. Hemophagocytosis and leukopenia were present in two of the four. Table 4 presents the clinical and laboratory profiles of deceased patients. Figure 1: presents Kaplan–Meier survival curve for pediatric patients diagnosed with HLH, stratified by type.

**Table 4:** The characteristics of patients who died from HLH (n=4)

| Patients | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Gender | F | M | F | M |
| Age (months) | 4 | 5 | 48 | 12 |
| Ferritin (ng/ml) | 550 | 5000 | 10000 | 20000 |
| Fibrinogen(mg/dl) | 180 | 145 | 48 | 128 |
| Triglyceride (mmol/l) | 1.3 | 5 | 8 | 6 |
| WBC(x10^9/L) | 37 | 15 | 2.9 | 2.5 |
| HB (g/dl) | 9 | 7 | 10.5 | 6 |
| Platelets (*10^3/mm3) | 260 | 370 | 120 | 120 |
| Presence of hemophagocyte in bone marrow | No | Yes | Yes | Yes |

Abbreviation: WBC: white blood cells, HB: hemoglobin, HLH: Hemophagocytic lymphohistocytosis, M: male, F: female

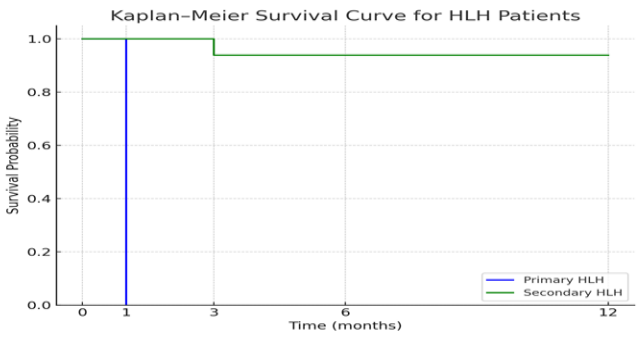


Figure 1. Kaplan–Meier survival curve for pediatric patients diagnosed with HLH, stratified by type

The blue line represents patients with primary HLH (n=2), both of whom died within the first month.

The green line represents patients with secondary HLH (n=33); 2 of them died within the first 3 months, while 31 survived until the end of the 12-month follow-up period.

No censored data points included

**Follow-up and Outcomes**

The median follow-up duration was approximately six months. No relapses were reported during this period. Most surviving patients showed clinical improvement with no evidence of long-term organ damage or neurodevelopmental sequelae.

**Comparative analysis**

Although a multivariate analysis was not performed due to the small sample size, elevated ferritin and triglyceride levels were common among deceased patients, suggesting potential prognostic relevance. A comparative analysis between deceased patients (n=4) and survivors (n=31) was conducted using non-parametric tests. The Mann–Whitney U test was applied for continuous variables, while Fisher's exact test was used for categorical variables. Deceased patients had significantly lower fibrinogen levels ($p = 0.04$) and higher triglyceride levels ($p = 0.03$). Although ferritin levels were notably elevated in this group, the difference was not statistically significant ($p = 0.09$). Leukopenia and hemophagocytosis in bone marrow were more common among the deceased ($p = 0.06$ and $p = 0.05$, respectively), but did not reach statistical significance.

**Organ Involvement**

Major organ involvement was limited in this cohort. Among the four deceased patients, all developed disseminated intravascular coagulation (DIC), liver injury with elevated liver enzymes, Two of these patients additionally experienced cardio-respiratory failure requiring vasopressor support and mechanical ventilation.

No cases of central nervous system involvement were documented. Systematic scoring of organ involvement (e.g., MAS-DS or HLH organ failure scores) was not performed, limiting the comprehensive assessment of disease severity.

**Treatment approach**

In our center, management focused in early immunosuppression using dexamethasone and etoposide, as access to newer targeted therapies

was limited, intravenous immunoglobulin (IVIG )was administered when clinically indicated and available.

## DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome that results in multiorgan failure and high mortality. Estimating the true prevalence and distribution of HLH is challenging due to the overlap of symptoms with other conditions, nonspecific diagnostic criteria, and frequent presence of comorbidities at diagnosis[1,13]. There is a significant gap in the literature concerning HLH in the Middle East, particularly in Jordan. Accordingly, this retrospective, single-center observational study aimed to characterize pediatric HLH cases in Jordan and to explore correlations between clinical and laboratory features and disease presentation.

Our study cohort included 35 pediatric patients (age range: 0–18 years; mean age: 6.1 months). Of them, 6% (n=2) had primary HLH and 94% (n=33) had secondary HLH. Primary HLH is generally classified based on genetic mutations—X-linked, autosomal recessive, or dominant—or in association with specific syndromes (e.g., Chediak-Higashi, Griscelli, and X-linked lymphoproliferative disorder)[24–25].

Clinically, HLH is characterized by persistent high fever, cytopenias, hyperlipidemia, hepatosplenomegaly, and hemophagocytosis on bone marrow examination[19,20]. In our study, leukopenia and thrombocytopenia were observed in 70% of patients, while anemia was found in 60%. These findings are consistent with results from the HLH-2004 trial, which reported bi-cytopenia in 92% of pediatric patients[18], and with a review by Ramos-Casals et al., who found thrombocytopenia and anemia in 80%, and leukopenia in 69% of adult patients with HLH [23].

Fever was the most common presenting symptom in our cohort, seen in 85% of patients, and skin rash was observed in 20%. These results align with the findings of Nandhakumar et al., who reported fever and skin rash in 100% and 24.4% of their patients, respectively[27]. Moreover, hyperferritinemia (>500 ng/mL) and hypofibrinogenemia (<150 mg/dL) were observed in 85% and 54% of our patients, respectively, which is comparable to Nandhakumar's findings of 96% and 42% [27]. However, organomegaly was documented in only 31% of our patients, markedly lower than the 68.6% reported by Nandhakumar et al. This discrepancy may be attributed to differences in diagnostic practices or the retrospective nature of our data.

Our laboratory findings were also comparable to those of a Korean retrospective study published in 2020[28]. In their cohort, hypertriglyceridemia was observed in 42% and elevated liver enzymes in 57% of patients. In our cohort, these values were 37% and 63%, respectively. Additionally, hemophagocytosis was observed in 31% of our patients, lower than the 91.4% reported in the Korean study, likely due to the predominance of secondary HLH in our population, many of which were associated with COVID-19 exposure.

While fever is a hallmark of HLH, cases of prolonged fever without an obvious cause are less commonly reported. Hakamifard et al. described a case of idiopathic HLH presenting as fever of unknown origin (FUO), which is defined as a temperature ≥38.3°C lasting more than three weeks without an identified source despite comprehensive evaluation [29–32]. HLH should be considered in the differential diagnosis of FUO, particularly when other clinical or laboratory features support the diagnosis.

Compared to other regional reports, our cohort demonstrated some differences. A Saudi study reported a higher rate of genetically confirmed primary HLH (over 80%) and a mortality rate of approximately 50%, significantly higher than our cohort's 11% [33,34]. In our study, only two patients had confirmed genetic mutations, likely due to limited access to genetic testing. A Turkish study also showed a higher prevalence of bone marrow hemophagocytosis and mortality (34%) than observed in our patients[35]. These differences may reflect variations in healthcare infrastructure, availability of advanced diagnostics, and population genetics.

## CONCLUSION

In conclusion, this retrospective study from King Abdullah University Hospital provides foundational data on the clinical features and laboratory findings of pediatric HLH in Jordan. Our results emphasize the

need for heightened clinical suspicion and early diagnosis to improve outcomes. Future multicenter studies with larger cohorts and genetic characterization are necessary to better define the epidemiology, pathogenesis, and optimal management of HLH in the region.

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