ORIGINAL ARTICLE

# Clinical Characteristics Treatment Approaches and Survival Outcomes in Secondary Hemophagocytic Lymphohistiocytosis: A Retrospective Observational Study

Amratansh Varshney[1], Pratibha Satish Phadke[2], Anusree Prabhakaran[3], Dipak Patade[4], Yash Bhalani[5], Abhishek Kumar[6*]

*Received:* 27 February 2025; *Accepted:* 23 May 2026

## Abstract

**Background:** Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal syndrome characterized by immune hyperactivation and a cytokine storm, leading to fever, cytopenia, organomegaly, and multiorgan dysfunction. Given its high morbidity and mortality, prompt diagnosis and treatment are essential. Currently, there are no established markers to predict outcomes in secondary hemophagocytic lymphohistiocytosis (sHLH).

**Materials and methods:** This retrospective study aimed to identify prognostic factors in patients with sHLH, specifically evaluating the prognostic role of absolute neutrophil count (ANC) and serum ferritin level. The study also examined the impact of dexamethasone and etoposide on the treatment of these patients.

**Results:** HLH remission was achieved in 64 patients (71.1%). Forty-seven out of those 64 patients survived and were discharged home, while 17 patients died in the hospital. HLH remission was not achieved in 26 patients (28.9%), of whom 25 patients died in the hospital. ANC at diagnosis and lower nadir ANC during the hospital stay significantly correlated with mortality ($p = 0.001$ and 0.017, respectively). Serum ferritin levels, however, were not a significant prognostic marker ($p = 0.396$). Treatment with dexamethasone was associated with better outcomes in patients with sHLH.

**Conclusion:** sHLH should be considered in patients with treatment-resistant bicytopenia or pancytopenia. Lower ANC at diagnosis and nadir ANC during hospitalization are associated with increased mortality, suggesting that ANC is a potential indicator for early immunochemotherapy. Serum ferritin level is not a significant prognostic marker. Early diagnosis and dexamethasone treatment help achieve HLH remission, which improves outcomes in sHLH. These findings highlight the need for prospective studies to better understand sHLH prognostic markers and therapeutic strategies, especially in intensive care settings, where mortality remains high.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1607

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled activation of the immune system, leading to a cytokine storm and subsequent multiorgan dysfunction.[1] This excessive immune response manifests clinically as fever, cytopenia, hepatosplenomegaly, and various neurological symptoms, often mimicking severe sepsis or other critical illnesses, thereby contributing to diagnostic challenges and potential underdiagnosis. HLH is broadly categorized into primary and secondary forms. Primary HLH, also known as familial HLH, typically presents in infancy or early childhood and is caused by inherited genetic mutations affecting the cytotoxic function of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs).[2] These genetic defects impair immune cells' ability to eliminate infected or damaged cells, leading to persistent macrophage activation and excessive cytokine production.[3] In contrast, secondary HLH, which is more commonly observed in adults, arises as a consequence of underlying triggers such as infections (particularly viral infections like Epstein–Barr virus and cytomegalovirus), malignancies (especially lymphomas), autoimmune diseases, and other inflammatory conditions.[1,4] Macrophage activation syndrome (MAS) represents a specific subset of secondary HLH that is closely associated with rheumatological disorders, including systemic juvenile idiopathic arthritis, systemic lupus erythematosus, and other autoimmune conditions.[5] While sharing many features with HLH, MAS may present with some distinct clinical and laboratory characteristics, such as less prominent cytopenia early in the disease course, more pronounced coagulopathy, and potentially higher levels of C-reactive protein. Furthermore, the cytokine profile in MAS may differ from that of HLH, with relatively greater elevations in interleukin-1β (IL-1β) and interleukin-6 (IL-6).[5] The pathogenesis of HLH involves a complex interplay of immune cells and cytokines. Dysfunctional NK cells and CTLs fail to effectively eliminate antigen-presenting cells, leading to the sustained activation of macrophages and the excessive release of proinflammatory cytokines, including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-18 (IL-18). This cytokine storm drives systemic inflammation, tissue damage, and the characteristic clinical manifestations of HLH.[6]

Given the aggressive nature of HLH and its potential for rapid deterioration, timely diagnosis and initiation of appropriate treatment are essential for improving patient outcomes. However, the diagnosis of HLH can be challenging because of the nonspecific nature of its clinical presentation and the lack of definitive diagnostic markers. The HLH-2004 diagnostic criteria, which include parameters such as fever, cytopenia, hyperferritinemia, and elevated levels of soluble interleukin-2 (IL-2) receptor, are widely used but may not always be sufficient for accurate diagnosis, particularly in atypical cases or those with underlying comorbidities.[7] Consequently, there is a pressing need for improved diagnostic and prognostic tools to guide clinical decision-making in HLH. This retrospective study was conducted to address this gap by investigating potential prognostic markers in patients with secondary hemophagocytic lymphohistiocytosis (sHLH). By identifying factors associated with patient outcomes, this study aimed to advance the understanding of sHLH and guide strategies for improving the management of this complex and often life-threatening condition.

[1]Senior Registrar; [2]Consulting Physician, Department of Internal Medicine; [3]Consultant, Department of Clinical Hematology; [4]Resident, Department of Cardiology, Deenanath Mangeshkar Hospital, Pune; [5]Consultant, Department of Critical Care Medicine, PD Hinduja Hospital, Mumbai, Maharashtra; [6]Associate Professor, Department of Cardiology, Government Superspeciality Hospital CIMS, Bilaspur, Chhattisgarh, India; *Corresponding Author

**How to cite this article:** Varshney A, Phadke PS, Prabhakaran A, *et al.* Clinical Characteristics Treatment Approaches and Survival Outcomes in Secondary Hemophagocytic Lymphohistiocytosis: A Retrospective Observational Study. J Assoc Physicians India 2026;74(7):e18–e23.

## Materials and Methods

### Study Design

This was a retrospective observational study of 90 patients with sHLH conducted at a tertiary care center in western India. The study duration was 3 years, starting in March 2020. The duration was extended because of the COVID-19 pandemic. All data were collected from the electronic medical records of patients diagnosed with sHLH (ICD-10: D76.3) from 2014 to 2020, confirmed on the discharge diagnosis.

### Study Aims and Objectives

The aim was to study the clinical profile and prognostic factors of patients with sHLH. The primary objective was to identify the prognostic role of serum ferritin level, absolute neutrophil count (ANC) at diagnosis, and nadir ANC in patients with sHLH. The secondary objective was to study the role of dexamethasone and etoposide in the outcomes of such patients.

#### *Inclusion Criteria*

A molecular diagnosis consistent with HLH.[4]

OR

Patients meeting five out of the following eight criteria:

- Fever >38.5°C.
- Splenomegaly.
- Cytopenia in ≥2 peripheral blood cell lines, that is, hemoglobin ≤9 gm/dL, platelet count <1,00,000/µL, and ANC <1,000/µL.
- Hypertriglyceridemia ≥265 mg/dL (fasting) or hypofibrinogenemia <150 mg/dL.
- Hemophagocytosis in bone marrow, spleen, or lymph node without evidence of malignancy.
- Low or absent natural killer (NK) cell activity.
- Elevated serum ferritin levels (≥500 µg/L).
- Elevated soluble CD25 (sCD25) levels (≥2,400 U/mL).

#### *Exclusion Criteria*

- Patient age <18 years.
- Patients with any primary bone marrow disorder known to produce cytopenia.
- Patients with a history of chemotherapy immediately before the onset of low blood counts.

### Data Collection and Statistical Analysis

This study was approved by the Institutional Thesis Review Committee and the Institutional Ethics Committee. It adhered to the 2013 revision of the Declaration of Helsinki and followed Committee on Publication Ethics (COPE) guidelines, prioritizing patient rights, safety, and well-being. The study was prepared in accordance with the STROBE guidelines for reporting observational studies, covering all 22 items and organized into Introduction (background, objectives), Methods, Results, Discussion, and Conclusions. Participation relied primarily on electronic data collection and imposed no financial burden on patients. It included all radiological, clinical, biopsy, and laboratory findings. Baseline evaluation of age, sex, clinical features such as splenomegaly and hepatomegaly, hemoglobin level, total leukocyte count, differential leukocyte count, ANC, serum glutamate oxaloacetate transferase, serum glutamate pyruvate transferase, prothrombin time international normalized ratio, blood urea, serum creatinine, hemophagocytosis in bone marrow biopsy, serum fibrinogen, and serum ferritin level was performed. Data were analyzed in terms of mortality according to the levels of ANC, nadir ANC, and serum ferritin. Statistical analysis of the data was performed using SPSS 28.0 statistical software (2021, IBM Co., NY, USA). Quantitative data are presented as arithmetic mean ± standard deviation (SD), and qualitative data as frequencies (%). Significance was set at $p < 0.05$. The unpaired Student's *t*-test was used to compare the means of two independent groups. For categorical variables, the Chi-squared test was used, or Fisher's exact test when cell counts were <5. Regression analysis was performed to identify determining factors and calculate odds ratios.

## Results

### Patients' Demography, Triggering/Risk Factors, and Clinical Features

This retrospective study at a tertiary care hospital in western India analyzed 90 HLH cases. Patients' demographics, triggering/risk factors, clinical features, and their correlation with outcomes are shown in Tables 1 and 2. Patients with secondary HLH ranged from 18 to 88 years of age (mean 46.44 ± 18.27 years); 57% were male ($n = 51$), and 43% were female ($n = 39$) (Table 1). Infections were the most common HLH trigger (75%, $n = 68$) (Fig. 1). Among these, dengue caused 13 cases (14.4%), viral fever 15 cases [with negative Epstein–Barr virus (EBV) serology in all 15 tested], sepsis 35 cases (38.9%), and fungal

**Table 1:** Demographic, clinical, and laboratory characteristics of the secondary HLH study population

| *Variables* | *Number (N = 90)/range (minimum and maximum)* | *Percentage/mean ± (SD)* |
|---|---|---|
| Sex (male) | 51 | 56.9% |
| Sex (female) | 39 | 43.1% |
| Fever | 85 | 94.4% |
| Splenomegaly | 55 | 61.1% |
| Hepatomegaly | 54 | 60.1% |
| Lymphadenopathy | 32 | 35.7% |
| Encephalopathy | 45 | 50.0% |
| Liver failure | 39 | 43.2% |
| Renal failure | 31 | 34.3% |
| Respiratory failure | 35 | 39.1% |
| Age | 18–88 years | 46.44 ± 18.27 years |
| Hemoglobin | 4.5–14.1 gm/dL | 8.6 ± 2.27 gm/dL |
| Total leukocyte count | 120–30,400 cmm | 5,119.9 ± 1,854.6 cmm |
| Platelet count | 4,000–3,13,000 cmm | 60,402.2 ± 1,475.8 cmm |
| ANC | 10–28,210 cmm | 2,576.2 ± 3,873.4 cmm |
| LDH | 232–21,820 U/L | 2,410.83 ± 4,606.5 U/L |
| Serum ferritin | 437–8,12,129 mg/mL | 38,918.45 ± 1,02,001.31 ng/mL |
| Serum fibrinogen | 30–650 mg/dL | 220.8 ± 140.8 mg/dL |
| Blood urea | 10–327 mg/dL | 71.11± 67.84 mg/dL |
| Serum creatinine | 0.4–7.2 mg/dL | 1.48 ± 1.46 mg/dL |
| SGOT | 10–24,800 U/L | 722.94 ± 2,988.51 U/l |
| SGPT | 10–5,280 U/L | 249.58 ± 686.52 U/L |
| ALP | 21–1,828 U/L | 305.70 ± 337.20 U/L |
| PT-INR | 1.0–15.0 | 5.8 ± 3.21 |
| Serum bilirubin | 0.43–32.98 mg/dL | 4.36 ± 5.62 mg/dL |
| Serum albumin | 1.22–4.29 gm/dL | 2.62 ± 0.648 gm/dL |

ALP, alkaline phosphatase; ANC, absolute neutrophil count; LDH, lactate dehydrogenase; PT-INR, prothrombin time–international normalized ratio; SGOT, serum glutamic oxaloacetic transaminase (AST); SGPT, serum glutamic pyruvic transaminase (ALT)

**Table 2:** Comparison of background clinical variables with the clinical outcome (mortality) in secondary HLH cases of the study

| | | *Good outcome (alive) (N = 47)* | | *Poor outcome (died) (N = 43)* | | *Total* | $\chi^2$ | *p-value* |
|---|---|---|---|---|---|---|---|---|
| | | *Count* | *Percent* | *Count* | *Percent* | | | |
| Gender | Male | 27 | 57.4 | 24 | 55.8 | 51 | 0.024 | 0.876 |
| | Female | 20 | 42.6 | 19 | 44.2 | 39 | | |
| Age category | <30 years | 14 | 29.8 | 8 | 18.6 | 22 | 9.497 | 0.091 |
| | 30–40 years | 12 | 25.5 | 4 | 9.3 | 16 | | |
| | 40–50 years | 8 | 17.0 | 9 | 20.9 | 17 | | |
| | 50–60 years | 5 | 10.6 | 4 | 9.3 | 9 | | |
| | 60–70 years | 5 | 10.6 | 11 | 25.6 | 16 | | |
| | >70 years | 3 | 6.4 | 7 | 16.3 | 10 | | |
| Splenomegaly | Present | 29 | 61.7 | 26 | 60.5 | 55 | 0.014 | 0.904 |
| | Absent | 18 | 38.3 | 17 | 39.5 | 35 | | |
| Hepatomegaly | Present | 30 | 63.8 | 24 | 55.8 | 54 | 0.601 | 0.438 |
| | Absent | 17 | 36.2 | 19 | 44.2 | 36 | | |
| Lymphadenopathy | Present | 15 | 31.9 | 17 | 39.5 | 32 | 0.569 | 0.451 |
| | Absent | 32 | 68.1 | 26 | 60.5 | 58 | | |
| Hepatic failure | Present | 19 | 40.4 | 20 | 46.5 | 39 | 0.339 | 0.561 |
| | Absent | 28 | 59.6 | 23 | 53.5 | 51 | | |
| Encephalopathy | Present | 15 | 31.9 | 30 | 69.8 | 45 | 12.870 | <0.001 |
| | Absent | 32 | 68.1 | 13 | 30.2 | 45 | | |
| Respiratory failure | Present | 13 | 27.7 | 22 | 51.2 | 35 | 5.220 | 0.022 |
| | Absent | 34 | 72.3 | 21 | 48.8 | 55 | | |
| Renal failure | Present | 11 | 23.4 | 20 | 46.5 | 31 | 5.310 | 0.021 |
| | Absent | 36 | 76.6 | 23 | 53.5 | 59 | | |

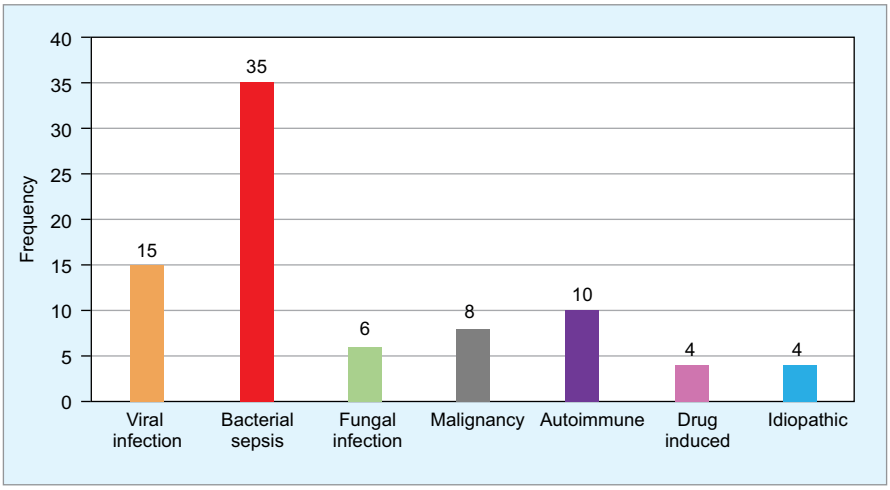


**Fig. 1:** Distribution of triggering/risk factors for secondary HLH among patients in the study cohort. Bar chart illustrating the frequency of various medical conditions diagnosed within the study population. Each bar represents a distinct condition, with the height corresponding to the number of cases recorded. This visualization highlights the predominance of infectious causes, particularly bacterial sepsis, in the clinical spectrum of the cohort. No statistical comparisons were applied in this figure

infections six cases (6.7%). Malignancy triggered eight cases (8.9%), and autoimmune diseases triggered 10 cases (11.1%), including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), autoimmune hemolytic anemia (AIHA), autoimmune hepatitis, and antiglomerular basement membrane (anti-GBM) disease. Other causes included drug-induced liver injury and methotrexate toxicity. Four cases (4.4%) were idiopathic. Fever (>38.5°C) occurred in 85 patients (94.4%) with secondary HLH, whereas five patients (5.6%) were afebrile. Splenomegaly affected 55 patients (61.1%), hepatomegaly 54 patients (60%), and lymphadenopathy 33 patients (36.7%) (Table 1); none correlated with mortality ($p = 0.90$, 0.43, and 0.45, respectively) (Table 2). Encephalopathy was seen in 45 patients (50%), hepatic failure in 39 patients (43.2%), renal derangement in 31 patients (34.3%), and respiratory failure in 35 patients (39.1%) (Table 1). Encephalopathy, respiratory failure, and renal derangement were significantly associated with mortality ($p < 0.001$, 0.022, and 0.021, respectively) (Table 2).

## Laboratory Findings

Patients' laboratory data and their correlation with outcomes are shown in Table 3. Anemia was observed [hemoglobin (Hb) <9 gm/dL] in 57 patients (63.8%; mean 8.6 ± 2.27 gm/dL, range 4.5–14.1 gm/dL); no association with mortality was found ($p = 0.342$). Leukopenia was present in 52 patients (57.7%), and neutropenia (ANC <1,000/µL) in 37 patients (41.1%); lower nadir ANC was associated with mortality ($p = 0.041$). Thrombocytopenia (<1,50,000/mm$^3$) was present in 73 patients (81.1%; $p = 0.811$). Hypertriglyceridemia (>265 mg/dL) was observed in 46 patients (51.5%), and hypofibrinogenemia (<150 mg/dL) in 35 patients (38.9%). Bone marrow hemophagocytosis was present in 53 of 90 patients (58.9%). Key mortality associations (Table 3) included higher blood urea ($p = 0.019$), serum creatinine ($p = 0.361$), serum glutamate oxaloacetate transferase (SGOT) ($p = 0.033$), serum glutamate pyruvate transferase (SGPT) ($p = 0.017$), total bilirubin ($p = 0.031$), direct bilirubin ($p = 0.022$), lower serum albumin

**Table 3:** Comparison of background laboratory variables with the clinical outcome (mortality) in secondary HLH cases of the study

| *Variables* | *Min value* | *Max value* | *Alive (mean ± SD)* | *Died (mean ± SD)* | *t-value* | *p-value* |
|---|---|---|---|---|---|---|
| Hemoglobin (gm%) | 4.5 | 14.1 | 8.9 ± 2.2 | 8.4 ± 2.1 | 0.95 | 0.342 |
| Total leukocyte count (per µL) | 200 | 3,73,130 | 8,420 ± 62,450 | 6,820 ± 8,200 | 0.18 | 0.856 |
| Platelet count (per µL) | 5,000 | 3,33,000 | 71,200 ± 68,900 | 66,800 ± 70,100 | 0.24 | 0.811 |
| ANC | 50 | 37,130 | 4,220 ± 3,270 | 2,880 ± 4580 | 2.17 | 0.032 |
| Nadir ANC (per µL) | 40 | 28,210 | 3,150 ± 2,610 | 1,440 ± 4,505 | 2.08 | 0.041 |
| Blood urea (mg/dL) | 10 | 327 | 51 ± 61 | 85 ± 84 | –2.38 | 0.019 |
| Serum creatinine (mg/dL) | 0.41 | 7.21 | 1.2 ± 1.6 | 1.5 ± 1.7 | –0.92 | 0.361 |
| SGOT (U/L) | 10 | 13,470 | 370 ± 850 | 1,050 ± 3,200 | –2.15 | 0.033 |
| SGPT (U/L) | 10 | 5,280 | 270 ± 430 | 820 ± 1,220 | –2.42 | 0.017 |
| ALP (U/L) | 21 | 1,828 | 390 ± 430 | 490 ± 580 | –1.12 | 0.265 |
| Total bilirubin (mg/dL) | 0.35 | 32.98 | 3.7 ± 5.8 | 6.8 ± 8.4 | –2.18 | 0.031 |
| Direct bilirubin (mg/dL) | 0.17 | 22.92 | 1.8 ± 3.2 | 4.1 ± 6.2 | –2.32 | 0.022 |
| Indirect bilirubin (mg/dL) | 0.08 | 10.06 | 1.9 ± 2.1 | 2.7 ± 2.8 | –1.58 | 0.117 |
| Serum proteins (gm/dL) | 2.7 | 7.95 | 5.7 ± 0.9 | 4.9 ± 1.4 | 3.12 | 0.002 |
| Serum albumin (gm/dL) | 1.49 | 4.25 | 2.8 ± 0.6 | 2.2 ± 0.7 | 4.45 | <0.001 |
| PT INR | 1.0 | >15 | 1.3 ± 0.6 | 2.0 ± 2.4 | –2.54 | 0.013 |
| Serum LDH (U/L) | 232 | 1,12,342 | 1,840 ± 7,420 | 12,340 ± 42,600 | –1.87 | 0.064 |
| Serum ferritin (ng/mL) | 257 | 2,09,870 | 19,250 ± 41,100 | 41,450 ± 55,800 | –1.93 | 0.061 |
| Serum TAG (mg/dL) | 61 | 1,307 | 350 ± 400 | 320 ± 250 | 0.43 | 0.669 |
| Serum fibrinogen (mg/dL) | 30 | 650 | 250 ± 140 | 200 ± 180 | 1.60 | 0.113 |

ALP, alkaline phosphatase; ANC, absolute neutrophil count; PT INR, prothrombin time international normalized ratio; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TAG, triglycerides

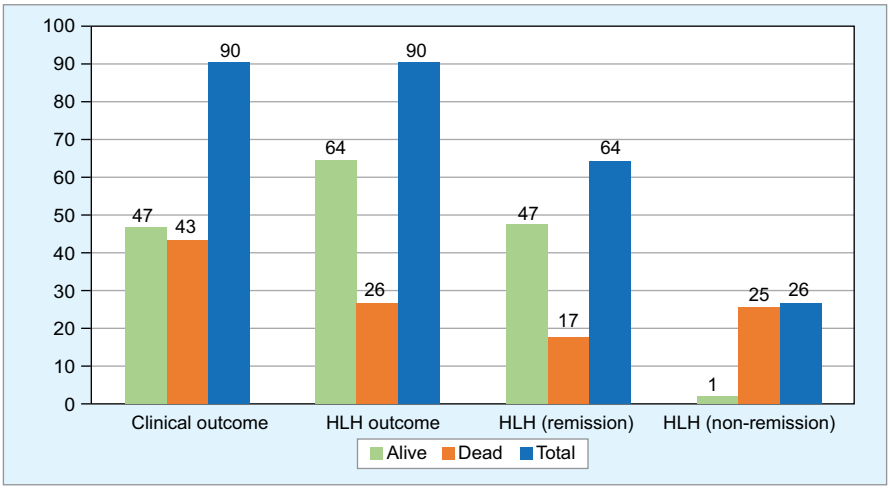


**Fig. 2:** Comparative outcome analysis of mortality across subgroups of secondary HLH in the study. Bar chart displaying the distribution of patient outcomes—categorized as alive/better (green), dead/poor (orange), and total (blue)—across four groups: overall clinical outcome, HLH outcome, HLH (improved) subgroup, and HLH (nonimproved) subgroup. This figure highlights the prognostic stratification within HLH patients, emphasizing significantly better survival in the improved subgroup. Data are presented as absolute counts. No statistical tests are shown in this figure

($p < 0.001$), and prothrombin time-international normalized ratio (PT-INR) ($p = 0.013$).

## Outcome

Overall, 47 patients (52.2%) were discharged from the hospital, whereas 43 patients (47.8%) died during hospitalization (Fig. 2). HLH remission was achieved in 64 patients (71.1%). Forty-seven out of 64 patients survived and were discharged home, while 17 patients died in the hospital (Fig. 2). However, HLH remission was not achieved in 26 patients (28.9%). Of these, 25 patients died in the hospital. Therefore, achieving HLH remission may reduce hospital mortality. Eighteen patients had an H score of <169, whereas 72 patients had an H score of ≥169. There was no significant correlation between mortality and H score ($p = 0.205$).

Patients were stratified by ANC at diagnosis into three groups (Fig. 3). In group A (ANC >1,500/cmm), 16 of 46 patients (34.8%) died. The association between lower ANC at diagnosis and higher mortality was statistically significant ($p = 0.032$) (Table 3). Grouping by nadir ANC during hospitalization showed similar trends. In group A, 20 of 29 patients (69.0%) died; in group B, six of 19 patients (31.6%) died; and in group C, 17 of 42 patients (40.5%) died (Fig. 3). Lower nadir ANC was significantly associated with increased mortality ($p = 0.041$) (Table 3). Patients were also categorized by serum ferritin levels. Group A (400–5,000 ng/mL) had 19 of 39 deaths (47.2%), group B (5,001–10,000 ng/mL) had five of 15 deaths (33.3%), and group C (> 10,000 ng/mL) had 19 of 36 deaths (52.8%) (Fig. 3). However, the correlation between ferritin levels and mortality was not statistically significant ($p = 0.061$) (Table 3).

Dexamethasone was administered to 70 patients (78%) (group A). Etoposide was added in 29 patients (33%) who were unresponsive to dexamethasone (group B). Twenty patients (23.3%) received neither agent (group C). Mortality was significantly higher in group C than in group A ($p = 0.002$) (Table 4), indicating a survival benefit with dexamethasone. No significant difference was observed between groups B and C ($p = 0.061$). HLH remission was achieved in 64

**Table 4:** Correlation between various treatment modalities, HLH improvement, and clinical outcome

| | | *Good outcome (alive) (N = 47)* | | *Poor outcome (died) (N = 43)* | | *Total* | $\chi^2$ | *p-value* |
|---|---|---|---|---|---|---|---|---|
| | | *Count* | *Percent* | *Count* | *Percent* | | | |
| Dexamethasone therapy vs no therapy | Yes | 43 | 91.5 | 27 | 62.8 | 70 | 10.701 | 0.002 |
| | No | 4 | 8.5 | 16 | 37.2 | 20 | | |
| Combination therapy vs no therapy | Yes | 11 | 23.4 | 18 | 41.9 | 29 | 3.502 | 0.061 |
| | No | 36 | 76.6 | 25 | 58.1 | 69 | | |
| HLH remission | Yes | 46 | 97.9 | 18 | 41.9 | 64 | 34.294 | <0.001 |
| | No | 1 | 2.1 | 25 | 58.1 | 26 | | |

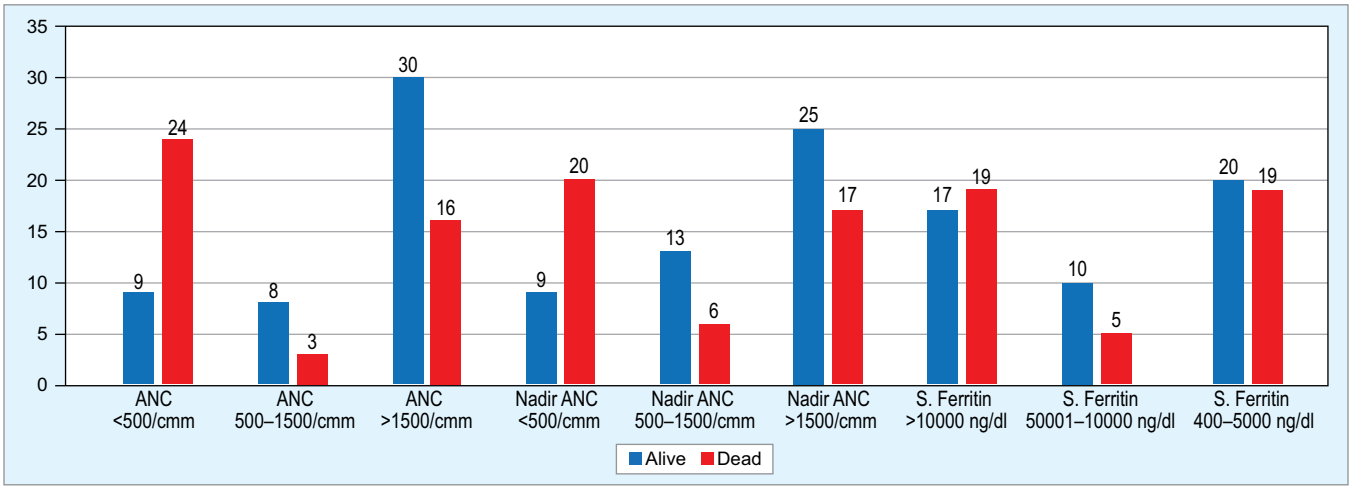


**Fig. 3:** Relationship between various objective laboratory parameters and patient survival outcomes. Bar chart comparing the number of patients who were alive (blue bars) vs dead (red bars) across nine clinical parameters. These include stratified ranges of ANC, nadir ANC, and serum ferritin levels. This figure highlights the association between immunologic and inflammatory markers and survival outcomes. Data are presented as absolute counts. No statistical tests are shown in this figure; ANC, absolute neutrophil count; cmm, cells per cubic millimeter; ng/dL, nanograms per deciliter

patients (71.1%), whereas 26 patients (28.9%) showed no response. Except for one patient, all nonresponders died in the hospital (Table 4), underscoring the importance of timely HLH treatment.

## Discussion

HLH is a rare and fatal disorder. In our study, 43 patients (47.8%) died in the hospital. No correlation of age or sex with mortality was observed. This is in concordance with studies conducted by Fazal et al. and Zhang et al.[4,8] We found that infections were the most common triggering factors in sHLH. Sepsis (approximately 38%) was a major triggering factor, followed by viral fever (approximately 17%). Malignancy, tuberculosis, and autoimmune disorders were also triggering factors in other cases identified in our study. As India is a tropical country, tropical illnesses are common. Infection-associated HLH was also the most common etiology (80%) in another study conducted by Rajagopala et al. in North India.[9] This is in contrast to Western countries, where malignancy, autoimmune disorders, and other noninfectious causes are the major causes of sHLH.[10,11]

In clinical presentation, fever (temperature >38.5°C) was very common in HLH patients (94.4%). Overproduction of interleukin-1 (IL-1) is responsible for high-grade fever and is generally unresponsive to conventional treatment. Hepatomegaly and splenomegaly were noted in approximately 60% of patients, and lymphadenopathy was present in 35%, but there was no statistically significant correlation of splenomegaly, hepatomegaly, or lymphadenopathy with mortality, as noted by Nair et al. in their study.[12] Acute kidney injury was seen in nearly one-third of the cases with sHLH and had a significant correlation with mortality, as observed in a study conducted by Aulagnon et al.[13] Encephalopathy is common in sHLH because of cytokine storms, which cause blood-brain barrier disruption and neuronal damage, and it signals poor outcomes by worsening multiorgan failure. It was observed in half of the patients and was statistically significantly associated with mortality in our study.

In laboratory parameters, bicytopenia occurred in approximately two-thirds of patients in our study. Hemophagocytosis in bone marrow, spleen, or lymph nodes aided HLH diagnosis; however, hemophagocytosis alone was not diagnostic because of its presence in infections (malaria, leishmaniasis) and rheumatological disorders.[14,15] Hypertriglyceridemia, secondary to reduced lipoprotein lipase from elevated tumor necrosis factor-alpha (TNF-α), was present in approximately 50% of cases, similar to the study conducted by Li et al.[16] Activated macrophages produce plasminogen activator, converting plasminogen to plasmin, which cleaves fibrinogen. Hypofibrinogenemia was seen in 40% of patients in our study, which was lower than that reported in the study by Signoff et al. (68%).[17] The hypofibrinogenemia group is expected to have a complicated course. In our study, hypoalbuminemia had a statistically significant correlation with patient outcome, which is in concordance with a study conducted by Parikh et al.[18]

In our study, ANC at the diagnosis of sHLH significantly correlated with mortality ($p = 0.032$), with lower neutrophil counts being associated with higher in-hospital mortality. Survivors had significantly higher ANC at

diagnosis (4,220 ± 3,270/μL) compared with nonsurvivors (2,880 ± 4,580/μL), suggesting that reduced ANC at presentation reflects profound immune dysregulation. This could stem from the HLH cytokine storm suppressing bone marrow granulopoiesis, thereby heightening susceptibility to opportunistic infections, a common trigger in sHLH linked to infections, malignancies, or autoimmune flares. Wang et al. analyzed 141 patients with sHLH and identified low ANC (≤1.21 × $10^9$/L) as an independent prognostic factor [hazard ratio (HR) 1.671, $p = 0.027$].[19] Integrating ANC with age, activated partial thromboplastin time (APTT), fibrinogen, and bleeding into a scoring model stratified 1-year survival as 66.4% (low risk), 40% (intermediate risk), and 2.3% (high risk; $p < 0.0001$).[20] Nadir ANC, the lowest neutrophil count during hospitalization, also showed a statistically significant association with outcomes ($p = 0.041$) in our study. Survivors maintained higher nadir ANC than nonsurvivors, with nadir ANC <500/cmm being linked to 69% mortality. Birndt et al. and Jordan et al. similarly found nadir neutrophil counts to be predictive of therapeutic response and survival in oncology patients, reinforcing the utility of this marker in HLH.[21,22] This underscores the prognostic value of nadir ANC, and monitoring nadir ANC could guide escalation to etoposide-based regimens (e.g., HLH-94/2004 protocols), especially in resource-limited settings such as India, where delays in aggressive therapy worsen outcomes.

Serum ferritin was also analyzed in our study. It was markedly elevated in both survivors and nonsurvivors. However, the difference lacked statistical significance ($p = 0.061$), indicating the unreliability of hyperferritinemia for mortality prediction despite its role as an HLH-2004 diagnostic criterion (>500 ng/mL).[7] Released by hyperactive macrophages, ferritin levels reflect inflammation severity but are confounded by infections, malignancies, liver dysfunction, iron overload, renal failure, hepatocellular injury, or hemolytic anemia, conditions that mimic or coexist with sHLH.[23] This nonspecificity limits its prognostic utility, favoring a diagnostic algorithm integrating H score or refined HLH criteria over ferritin alone.[20] These findings align with Schram et al., who studied 113 patients with sHLH and found extreme hyperferritinemia (>50,000 ng/mL) in non-HLH mimics, with low predictive value for adult HLH.[24] Carol et al. highlighted ferritin's role in HLH/hyperinflammation, linking it to iron-mediated damage and advocating interleukin-18 (IL-18)/sCD25 biomarkers, plus real-time interferon-induced hyperinflammation (IFH) screening and vascular signatures in sepsis.[25] Conversely, Koymen et al. reported in 99 patients with secondary hemophagocytic syndrome (HPS)/HLH in the intensive care unit (ICU) that early ferritin reduction predicted survival (multivariate HR 0.62, $p = 0.02$).[26] Overall, ANC and nadir ANC emerged as robust prognostic tools in sHLH, whereas ferritin, although diagnostically important, showed limited prognostic value because of confounding factors. A multifactorial approach incorporating ANC trends, clinical triggers, and rapid genetic testing may optimize risk stratification, particularly in cardiothoracic or oncology settings where HLH complicates care.

Our retrospective study of 90 patients with sHLH identified strong associations between therapeutic interventions and survival outcomes. Dexamethasone therapy was significantly associated with survival, with 91.5% of survivors receiving it compared with 62.8% of nonsurvivors. The most powerful predictor of survival was clinical remission of HLH. Combination therapy with dexamethasone and etoposide showed only borderline significance ($\chi^2 = 3.502$, $p = 0.061$), with a higher proportion of nonsurvivors (41.9%) than survivors (23.4%) receiving it. This suggests that etoposide may not enhance, and could potentially attenuate, the benefit in this cohort, possibly because of its use in more critically ill patients. These findings are consistent with the HLH-2004 protocol, which reported remission rates of 50–70% with dexamethasone-etoposide regimens, although etoposide intensification was associated with poor salvage outcomes in refractory disease.[27] Wu et al., in their review article, showed that dexamethasone's anti-inflammatory effects are particularly valuable in cardiac HLH, where cytokine storms can exacerbate myocardial injury, especially after myocardial infarction or percutaneous coronary intervention.[28,29] In contrast, Escoto et al. documented the known cardiotoxicity of etoposide, including arrhythmias and cardiomyopathy in 5–10% of regimens, which may limit its utility in this population.[30,31] Dexamethasone monotherapy should be prioritized as frontline treatment for cardiac HLH, especially in resource-limited settings. Its strong anti-inflammatory effects and favorable safety profile enable rapid stabilization against cytokine storm and cardiac failure.

### Limitations

This retrospective, single-center study is subject to selection and information bias. Epstein–Barr virus (EBV) serology was available for only a few patients despite its key role in HLH, and inconsistent measurements of NK cell activity and soluble CD25 limited prognostic analysis. Additional constraints include limited generalizability to diverse Indian settings; confounders (e.g., age, comorbidities, and H score); small subgroups (e.g., the "no therapy" group) requiring Fisher's exact tests; incomplete workups (e.g., variable ferritin measurements and missing biopsies) that hindered HLH-2004/2018 assessments; and the absence of long-term follow-up for relapse and survival. Prospective, multicenter trials with propensity matching and standardized biomarkers are needed to validate these findings and refine HLH algorithms in resource-constrained environments.

## Conclusion

This study concludes that HLH is rare, often fatal, and requires early diagnosis to improve patient outcomes. Clinicians should suspect HLH in patients with treatment-resistant bicytopenia or pancytopenia. Lower ANC at diagnosis and lower nadir ANC during hospitalization correlated with increased mortality, indicating that ANC may serve as a potential marker for the early initiation of immunochemotherapy. Since hyperferritinemia can result from multiple conditions and did not correlate with mortality in this study, very high serum ferritin levels may be used as a diagnostic marker rather than a prognostic marker. Dexamethasone and early initiation of etoposide may help improve cytopenia and prognosis in sHLH.

## Author Contributions

All authors contributed to the study conception, design, data collection, data analysis, or manuscript drafting. All authors reviewed and approved the final manuscript.

## Data Availability

Data are available by contacting the corresponding author.

## Ethical Approval

The study was approved by the Institutional Ethics Committee and adhered to established international ethical standards.

## Consent to Participate

Written or verbal informed consent was obtained from patients or their relatives for anonymized patient information to be published in this article.

## References

1. Karlsson T. Secondary haemophagocytic lymphohistiocytosis: experience from the Uppsala

University Hospital. Ups J Med Sci 2015;120(4):257–262.
2. Malinowska I, Machaczka M, Popko K, et al. Hemophagocytic syndrome in children and adults. Arch Immunol Ther Exp (Warsz) 2014;62(5):385–394.
3. Shabrish S, Kelkar M, Yadav RM, et al. The spectrum of clinical, immunological, and molecular findings in familial hemophagocytic lymphohistiocytosis: experience from India. Front Immunol 2021;12:612583.
4. Fazal F, Gupta N, Soneja M, 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.
5. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med 2013;11:185.
6. Bseiso O, Zahdeh A, Isayed O, et al. The role of immune mechanisms, inflammatory pathways, and macrophage activation syndrome in the pathogenesis of hemophagocytic lymphohistiocytosis. Cureus 2022;14(12):e33175.
7. La Rosée P, La Rosée F. HLH: diagnostics revisited and improved. Blood 2024;144(22):2274–2275.
8. Zhang FJ, Huang GQ, Li J, et al. Clinical characteristics of adult hemophagocytic lymphohistiocytosis in the emergency department. Int J Gen Med 2021;14:4687–4694.
9. Rajagopala S, Singh N, Agarwal R, et al. Severe hemophagocytic lymphohistiocytosis in adults—experience from an intensive care unit from North India. Indian J Crit Care Med 2012;16(4):198–203.
10. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. Blood Res 2021;56(S1):S17–S25.
11. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med 2014;5:69–86.
12. Nair V, Das S, Sharma A, et al. A clinicopathological analysis of 26 patients with infection–associated haemophagocytic lymphohistiocytosis and the importance of bone marrow phagocytosis for the early initiation of immunomodulatory treatment. Postgrad Med J 2013;89(1050):185–192.
13. Aulagnon F, Lapidus N, Canet E, et al. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. Am J Kidney Dis 2015;65(6):851–859.
14. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program 2013;2013:605–611.
15. Zoller EE, Lykens JE, Terrell CE, et al. Hemophagocytosis causes a consumptive anemia of inflammation. J Exp Med 2011;208(6):1203–1214.
16. Li X, Yan H, Luo T, et al. Fulfillment status of hypertriglyceridemia and hypofibrinogenemia in children with hemophagocytic lymphohistiocytosis and risks of multiple organ dysfunction syndrome and early mortality. Orphanet J Rare Dis 2022;17(1):161.
17. Signoff JK, Fitzgerald JC, Teachey DT, et al. Hypofibrinogenemia is associated with poor outcome and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome in pediatric severe sepsis. Pediatr Crit Care Med 2018;19(5):397–405.
18. Parikh SA, Kapoor P, Letendre L, et al. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. Mayo Clin Proc 2014;89(4):484–492.
19. Wang S, Lv K, Zhou Y, et al. A novel prognosis–prediction model based on coagulation indicators in secondary hemophagocytic lymphohistiocytosis. Ann Hematol 2023;102(11):3251–3259.
20. Lachmann G, Heeren P, Schuster FS, et al. Multicenter validation of secondary hemophagocytic lymphohistiocytosis diagnostic criteria. J Intern Med 2025;297(3):312–327.
21. Birndt S, Schenk T, Heinevetter B, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. J Cancer Res Clin Oncol 2020;146(4):1065–1077.
22. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118(15):4041–4052.
23. Wang J, Pantopoulos K. Regulation of cellular iron metabolism. Biochem J 2011;434(3):365–381.
24. Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. Blood 2015;125(10):1548–1552.
25. Carol HA, Mayer AS, Zhang MS, et al. Hyperferritinemia screening to aid identification and differentiation of patients with hyperinflammatory disorders. J Clin Immunol 2024;45(1):4.
26. Koymen G, Kilincer Bozgul SM, Kurtulmus IA, et al. Dynamic ferritin levels and survival outcomes in secondary hemophagocytic syndrome: a comprehensive analysis. Front Med (Lausanne) 2025;12:1517101.
27. El-Cheikh J, Moukalled N, Malard F, et al. Cardiac toxicities in multiple myeloma: an updated and a deeper look into the effect of different medications and novel therapies. Blood Cancer J 2023;13(1):83.
28. Wu Y, Sun X, Kang K, et al. Hemophagocytic lymphohistiocytosis: current treatment advances, emerging targeted therapy and underlying mechanisms. J Hematol Oncol 2024;17(1):106.
29. Kumar DA, Muneer DK, Qureshi DN. Relationship between high sensitivity troponin I and clinical outcomes in non–acute coronary syndrome (non–ACS) acute heart failure patients—a one-year follow-up study. Indian Heart J 2024;76(2):139–145.
30. Escoto H, Ringewald J, Kalpatthi R. Etoposide–related cardiotoxicity in a child with haemophagocytic lymphohistiocytosis. Cardiol Young 2010;20(1):105–107.
31. Kumar A, Gupta M, Varshney A, et al. Flecainide fallout: a rare case report of refractory ventricular tachycardia and updated management strategies. Eur Heart J Case Rep 2025;9(8):ytaf368.