ORIGINAL ARTICLE

# Clinical Profile, Treatment, and Outcome of Patients with Secondary Hemophagocytic Lymphohistiocytosis in Critically Ill Patients: A Prospective Observational Study

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## Abstract

**Introduction:** The objective of the study was to evaluate the clinical profile and outcome of patients with secondary hemophagocytic lymphohistiocytosis (HLH) in critically ill patients.

**Materials and methods:** A prospective observational study was conducted where critically ill adult patients presenting with fever and bicytopenia were evaluated according to the HLH-2004 diagnostic criteria for the presence of secondary HLH. The underlying trigger, clinical profile, treatment, and outcome of patients with HLH were analyzed.

**Results:** Of the 76 critically ill patients with fever and bicytopenia, 33 (43%) patients were diagnosed with HLH. The following triggers for HLH were identified: bacterial infections (23%), fungal infections (10%), viral infections (10%), parasitic infections (10%), autoimmune diseases (13%), and malignancy (8%). A total of 78% of the HLH cases received steroids, but the use of steroids was not associated with improvement in mortality.

**Conclusion:** There is a high prevalence of HLH in patients presenting with fever and bicytopenia in critically ill adult patients. Infections were identified as the most common trigger of HLH.

**Keywords:** BM score, Ferritin, Hemophagocytic lymphohistiocytosis, H score, Infection.

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## Introduction

Hemophagocytic lymphohistiocytosis (HLH) has been described as a hyperinflammatory state with a characteristic dysregulated activation of cytokines leading to florid clinical manifestations. It was first recognized in children as a familial immune dysregulation disorder.[1,2] Eventually, triggers such as infections or malignancies were identified that can give similar manifestation as familial HLH. To differentiate it from familial HLH, this syndrome was designated as secondary HLH. Although there is an abundance of literature on primary HLH, the literature on secondary HLH in adults is scarce. HLH is diagnosed according to the HLH 2004 diagnostic criteria where a combination of five out of the eight criteria needs to be fulfilled.[3] The presence of individual criterion in isolation is not helpful in diagnosis but rather the combination of all criteria is what makes HLH more likely. The treatment of secondary HLH includes treatment of the underlying triggers along with immunosuppressive agents such as steroids, etoposide, and cyclosporine. The aim of this study was to identify the triggers and delineate the clinical epidemiology and outcome of critically ill patients diagnosed with HLH.

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## Materials and Methods

This was a prospective observational study conducted in the medical ward and intensive care unit (ICU) at a tertiary care institute in Northern India for a period of 2 years (2017–2018). The study was initiated after obtaining ethical clearance from the Institute's ethics committee. A total of 76 critically ill patients with fever and bicytopenia (hemoglobin <13 gm/dL for male and <12 gm/dL for female, leucocyte count <4,000/mm$^3$, platelet count <100,000/mm$^3$) were recruited for the study. Patients admitted with a diagnosed infectious cause, or hematological malignancies were excluded. Patients who fulfilled any five out of the eight criteria of HLH-2004 diagnostic criteria were diagnosed as HLH.[3] Bone marrow score (BM score) and H score were also calculated for all the cases. Relevant investigations were carried out to identify the triggers (tropical infections, malignancies, autoimmune diseases, etc.) for HLH. The management of all recruited patients was done by physicians who were not a part of the study. The total duration of hospitalization and outcome was recorded.

Data were recorded in a predesigned case record form and managed on an excel spreadsheet. Data collected were analyzed

by frequency (percentage), mean (SD), and median (interquartile range). A categorical variable was compared by Chi-square/Fisher exact test. A continuous variable was compared by independent *t*-test or Wilcoxon rank-sum test. Sensitivity and specificity of BM score and H score were calculated for the Indian population. A receiver operator characteristic (ROC) curve was generated to look for the cut-off ferritin value that can be used to identify HLH. Univariate analysis was carried out to find the predictors of mortality in patients with HLH. A *p*-value of <0.05 was considered statistically significant. Statistical analysis was done by STATA 14 software for Windows.

## Results

Of the 76 critically ill patients with fever and bicytopenia, a total of 33 (43.4%) (95% CI, 32–54.8%) patients were diagnosed with HLH based on the HLH criteria. No significant difference in the baseline parameters of patients diagnosed with or without HLH was noted (Table 1). The individual criteria of HLH-2004, BM score and H-score in the recruited patients have been tabulated in Table 2. The sensitivity and specificity of BM score in diagnosing HLH in our study was 90.9 and 37.2%, respectively. In comparison to the BM score, H score had a better specificity (81.8%) than sensitivity (55.8%). On ROC analysis, a ferritin value of >2,000 ng/mL had a sensitivity and specificity of only 63.4 and 47.6%, respectively, in diagnosing HLH. The area under the curve was 0.6053.

Of the 33 patients with HLH, triggers for HLH could be identified in only 23 patients. Of these 23 patients, six patients had more than one triggers. The following etiologies were identified as triggers: infections ($n = 21$), autoimmune ($n = 5$), and malignancy ($n = 3$) (Table 3). Use of steroids was seen in 23/33 patients out of which 18 received steroids in dosage according to the HLH 2004 protocol (Table 3). Etoposide ($n = 3$), cyclosporine ($n = 1$), and intravenous immunoglobulin ($n = 2$) were used sparingly with steroids. A total of 13 patients with HLH succumbed to the illness. No significant predictors of mortality could be identified (Table 4). Use of steroids was not associated with improvement in rates of mortality (Table 4). There was no statistical difference between the patients identified as HLH and those without HLH in terms of mortality (41.8 vs 39.3%, $p = 0.82$) and mean duration of hospital stay (18 vs 17 days, $p = 0.43$).

## Discussion

To the best of our knowledge, this is the first prospective study of HLH from India. The study identified the frequency of patients diagnosed with HLH (as per HLH 2004 criteria) among patients presenting to medical wards/ICUs with fever and bicytopenia as 43.4%. Fever and bicytopenia were taken as the inclusion criteria to identify as many patients with HLH that was possible with limited resources. Since ours is an apex care center that receives referrals from secondary and tertiary care hospitals, most of the patients

**Table 1:** Baseline clinical and laboratory parameters of recruited patients

| *Clinical parameters* | *HLH n = 33* | *Not HLH n = 43* | *p value* |
|---|---|---|---|
| Gender distribution | Male: 19 (58%) | Male: 17 (39.5%) | 0.118 |
| Age* | 31 ± 14 | 32.4 ± 14.3 | 0.642 |
| Sequential organ failure assessment score# | 5 (3–6) | 6 (3–9.25) | 0.142 |
| Jaundice | 11 (33.3%) | 13 (30.2%) | 0.77 |
| Loss of weight | 17 (51.5%) | 16 (38.1%) | 0.24 |
| Breathlessness | 22 (66.6%) | 32 (76.1%) | 0.36 |
| Altered sensorium | 9 (27.2%) | 12 (27.9%) | 0.95 |
| Rash | 3 (9%) | 6 (14.2%) | 0.72 |
| Hepatomegaly | 21 (63.6%) | 18 (41.8%) | 0.06 |
| Lymphadenopathy | 5 (15.1%) | 7 (16.2%) | 0.89 |
| Shock | 10 (30.3%) | 21 (48.8%) | 0.10 |
| *Laboratory parameters* | | | |
| Hemoglobin (gm/dL)* | 7.07 ± 1.99 | 7.53 ± 1.96 | 0.31 |
| Total leukocyte count (cells/mm$^3$)# | 3,500 (1,850–7,600) | 3,800 (2,400–14,600) | 0.24 |
| Platelet count (cells/mm$^3$)# | 42,000 (23,000–71,500) | 40,000 (17,000–70,000) | 0.54 |
| Erythrocyte sedimentation rate* | 52.53 ± 17.7 | 57.15 ± 15.3 | 0.28 |
| Serum creatinine (mg/dL)* | 1.17 ± 1.30 | 138.6 ± 7.0 | 0.26 |
| Aspartate transaminase (U/L)# | 88 (52–163.5) | 3.91 ± 0.72 | 0.47 |
| Alanine transaminase (U/L)# | 60 (21–99) | 37 (17–59) | 0.67 |
| Prothrombin time (international normalized ratio)* | 1.38 ± 0.26 | 1.96 ± 0.40 | 0.09 |
| Total cholesterol (mg/dL)* | 114.09 ± 53.93 | 97.87 ± 32.90 | 0.12 |
| Ferritin (mg/dL)# | 2,000 (1,391–5,959) | 2000 (623.5–3536.75) | 0.11 |
| Lactate dehydrogenase (U/L)# | 717 (495–1,177) | 636 (304–1,073) | 0.27 |
| Fibrinogen (mg/dL)* | 321.6 ± 162.7 | 336.7 ± 133.8 | 0.68 |
| Triglyceride (mg/dL)* | 321.9 ± 140.3 | 253.1 ± 162.5 | 0.46 |

*Mean is expressed as Mean ± Standard deviation and #Median is expressed with interquartile range in brackets

**Table 2:** Individual criteria of HLH, BM score, and H score in patients with HLH

| *Parameters* | *HLH n = 33 (%)* | *Not HLH n = 43 (%)* |
|---|---|---|
| Fever | 33 (100%) | 40 (93.0) |
| Bicytopenia | 33 (100%) | 36 (83.7) |
| Splenomegaly | 28 (84.8) | 20 (46.5) |
| Hyperferritinemia (>500 mg/dL) | 32 (96.9) | 34 (79.0) |
| Hypertriglyceridemia (>265 mg/dL) | 26 (78.7) | 16 (37.2) |
| Hypofibrinogenemia (<150 mg/dL) | 5 (15.1) | 2 (4.6) |
| Hemophagocytosis (*n* = 45) | 14/25 (56.0) | 3/20 (15.0) |
| Low NK cell activity (*n* = 62) | 12/22 (54.5) | 2/40 (5.0) |
| BM score (≥10) | 30 | 27 |
| BM score (<10) | 3 | 16 |
| H score (<169) | 6 | 24 |
| H score (≥169) | 27 | 19 |

**Table 3:** Triggers of secondary HLH identified in the study

| | | |
|---|---|---|
| Infections (*n* = 21) | Bacterial (*n* = 9) | Enteric fever (4) |
| | | Endocarditis (1) |
| | | Tuberculosis (3) |
| | | Scrub typhus (1) |
| | Fungal (*n* = 4) | Aspergillosis (3) |
| | | Mucormycosis (1) |
| | Viral (*n* = 4) | Herpes encephalitis (2) |
| | | Dengue (1) |
| | | HIV (1) |
| | Parasites (*n* = 4) | Malaria (2) |
| | | Leishmania (2) |
| Malignancy (*n* = 3) | | Lymphoma (3) |
| Autoimmune (*n* = 5) | | Systemic lupus erythematosus (3) |
| | | Thrombotic thrombocytopenic purpura (1) |
| | | Sjogren syndrome (1) |
| Unknown (*n* = 10) | | |

were critically ill at the time of presentation. This explains the higher prevalence of HLH in our study.

A total of five or more criteria were met in 33 patients. Splenomegaly was seen in 94% of the patients. The mechanism of splenomegaly in HLH involves lymphocytic and histiocytic infiltration. Besides, splenomegaly can also be a part of the underlying diseases such as lymphoma or other infections. Ferritin, which is secreted by activated macrophages, is an established marker for HLH activity.[4] The HLH-2004 criterion of 500 ng/mL has shown to have a sensitivity of 84% in patients with the familial disease. In some studies, higher ferritin values varying from 3,000 or 30,000 were considered in an attempt to improve the probability of accurately diagnosing HLH.[5] In our study, ferritin levels were not helpful to discriminate HLH patients from those without HLH with an area under ROC curve = 0.6053.

**Table 4:** Predictors for mortality in patients with HLH

| *Characteristics* | *Death n = 13 (%)* | *No death n = 20 (%)* | *p value* |
|---|---|---|---|
| Fever | 13 (100) | 19 (95.0) | 0.99 |
| Bicytopenia | 13 (100) | 18 (90.0) | 0.50 |
| Hyperferritinemia | 13 (100) | 19 (95.0) | 0.99 |
| Splenomegaly | 12 (92.3) | 16 (80.0) | 0.62 |
| Fibrinogen | 2 (15.3) | 3 (15.0) | 0.99 |
| Hypertriglyceridemia | 9 (69.2) | 17 (85.0) | 0.39 |
| BM hemophagocytosis (*n* = 25) | 5 (45.4) | 9 (64.2) | 0.34 |
| Low NK cell activity (*n* = 22) | 5 (55.5) | 7 (53.8) | 0.99 |
| Steroids given | 9 (69.2) | 14 (70.0) | 0.99 |
| Steroids given in HLH-2004 dosage | 6 (46.1) | 12 (60.0) | 0.43 |
| Mechanical ventilation | 5 (38.4) | 3 (15.0) | 0.21 |
| Shock | 6 (46.1) | 4 (20.0) | 0.13 |
| Dialysis | 1 (7.6) | 2 (10.0) | 0.99 |
| Unknown diagnosis | 6 (46.1) | 4 (20.0) | 0.10 |
| BM score >10 | 12 (92.3) | 18 (90.0) | 0.99 |
| H score >169 | 10 (76.9) | 17 (85.0) | 0.65 |

A total of 78.7% of patients had hypertriglyceridemia, which is explained by an increase in TNF alpha, which inhibits lipoprotein lipase. Hemophagocytosis in bone marrow was seen in 56% of the patients with HLH. It is pertinent to note that presence of hemophagocytosis is not enough to make a diagnosis of HLH as it can be seen in other conditions like influenza, leishmaniasis, malaria, and active rheumatologic disorders.[6] In a study by Goel et al., hemophagocytosis had a sensitivity and specificity of 83 and 60% to eventually diagnose HLH. This specificity can be increased to 100% by the introduction of a numerical cut-off to the number of hemophagocytosis seen in the sample.[7] In our study, only 15% of HLH patients had hypofibrinogenemia, which is less compared to a Chinese study which reported 69.4% of its adult HLH patients having hypofibrinogenemia.[8] Decreased fibrinogen value is due to secretion of high levels of plasminogen activator by macrophages leading to increased concentrations of plasmin, which in turn cleaves fibrinogen. Low NK cell activity in our study was seen in 54% of the patients with HLH. Due to unavailability of NK cell activity testing in every center, diagnosis may get delayed. But treatment should not be delayed awaiting NK cell activity as immunosuppressive therapy does not impair the assay performance of CD107a.[9] It should be noted that the criterion is the impaired activity of each of the NK cells, not the low number of the normal NK cells.[10]

Infectious triggers were more common in our cohort. In our study, 53% of individuals were found to have one or the other infection. Similar to other published studies, tropical infections like malaria, tuberculosis, enteric fever, rickettsial diseases, dengue, and leishmaniasis were found to be common triggers.[11] A large proportion of the study population (26%) patients remained undiagnosed, despite being thoroughly investigated.

There was a mortality of 39.3% in patients with HLH, which was similar to another study by Gualdoni et al.[12] The management of HLH requires collaboration among intensivists, hematologists, infectious disease specialists, and pathologists.[11] The mainstay of successful management of secondary HLH is the treatment of the

underlying etiology, especially infections.[13] All our patients were initiated on definitive therapy. Although corticosteroids have also shown to be effective in the treatment of adult onset secondary HLH, the use of steroids was not associated with significant improvement in mortality.[14] Although early use of etoposide is associated with good results in rapidly progressing HLH, in our study, the outcome was unfavorable in all the three patients in whom it was used.[15,16] The ineffectiveness of immunosuppressive agents in our study may have been related to a higher prevalence of infections in our studies. High-dose immunosuppressive agents may complicate the underlying infection and lead to the proliferation of infectious agent.

## Limitations

The study was limited by the small number of patients. EBV as a cause was not evaluated due to the unavailability of the testing facility. Treatment, according to 2004, HLH protocol was not followed in all patients.

In conclusion, there is a high percentage of critically ill individuals who fulfil the criteria of HLH in patients with fever and bicytopenia. Infection is the most common trigger in patients from tropical countries. There is a need for larger studies to evaluate the usefulness of steroids and immunosuppressive agents in such patients.

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