Clinical Features and Prognostic Factors of Early Outcome in Pediatric Hemophagocytic Lymphohistiocytosis: A Retrospective Analysis of 227 Cases

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Summary: Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening clinical syndrome in children, and the knowledge of it is still limited. Two hundred twenty-seven children with HLH in our hospital were retrospectively analyzed from January 2001 to December 2018. The age of the patients on admission ranged from 1 day to 14 years old. The 3 most common clinical manifestations include fever (98.7%), hepatomegaly (88.6%), and splenomegaly (92.1%). The decrease of high-density lipoprotein cholesterol (99.1%) is very common in children with HLH. Albumin < 25 g/L, activated partial thromboplastin time > 65 s, and lactose dehydrogenase > 1000 U/L were independent risk factors for poor early prognosis in children with HLH, and their odds ratio values were 2.515, 3.094, and 2.378, respectively, while age > 28 months was identified as a protective factor (odds ratio = 0.295). Of the 227 children, 67 (29.52%) died within 30 days of onset. The mortality rate in 2013 to 2018 was significantly lower than that in 2001 to 2012 (16.35% vs. 40.65%, P = 0.000). The shortening of the time from onset to admission and the reduction of time from admission to definitive diagnosis could be some of the reasons for the decrease of HLH mortality in 2013 to 2018 (P < 0.05, respectively). Our study suggests that early identification of risk factors for HLH, timely diagnosis and treatment are important measures to improve the short-term prognosis of HLH in children.

Key Words: hemophagocytic lymphohistiocytosis, clinical features, children, prognostic factors, early outcome

Original Article

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Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening clinical syndrome characterized by a large number of inflammatory reactions, cytokine storms, and multiple organ involvement.1,2 HLH has diverse and atypical clinical manifestations, rapid disease progression, and high mortality. The mortality rate of children with HLH is about 8% to 22%.3 Research on the clinical characteristics and prognostic factors of HLH in children will help improve the treatment level of this rare disease.

Materials and Methods

Patients and Diagnosis

A retrospective analysis on children with HLH was carried out from January 1, 2001, to December 31, 2018, at the Pediatric Department of the Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University. Two periods, 2001 to 2012 and 2013 to 2018, were covered in the study. According to HLH-2004 guidelines, all patients below 18 years fulfilled at least 5 of the 8 required criteria.4 For critically ill patients, supportive treatment such as blood transfusions, mechanical ventilation, high-dose intravenous immunoglobulin (IVIG), and glucocorticoids were given. For patients with infections related to the available targeted drugs, corresponding anti-infection treatment was given. For the children who obtained the informed consent of their guardians, chemotherapy was carried out according to the HLH-1994 or HLH-2004 regimen. A total of 227 patients were included in this study and all patients were divided into a nonsurvivor group and survivor group, based on whether the patient passed away within 30 days of the onset. Due to technical reasons, natural killer cell activity and sCD25-related tests were not carried out in our hospital.

We analyzed age, sex, clinical outcome, clinical manifestations, treatment, number of days with fever, number of days from admission to diagnosis, leukocyte (Neu), and platelet counts, hemoglobin, serum ferritin levels, fibrinogen, triglycerides, the presence of bone marrow hemophagocytosis, the proportion of natural killer cells, alanine aminotransferase, serum sodium, serum albumin, C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, total cholesterol, lactose dehydrogenase (LDH), activated partial thromboplastin time (APTT), prothrombin time, and thrombin time in these patients.

This study was approved by the ethics committee of the Second Affiliated Hospital of Wenzhou Medical University (ethical approval number: LCKY2020-194).

Statistical Analysis

All data analyses were performed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL). Descriptive statistics were expressed as numerical values, percentages, arithmetic mean (± s), and median with interquartile
range. The mean or median was used to fill in missing values. Intergroup differences were assessed by the χ² test or Fisher exact test. Analysis of variance was used to test the intergroup homogeneity of variance. The comparison between 2 groups of normal distribution measurement data was done by independent sample t test, and the comparison between groups of non-normal distribution measurement data was performed using Mann-Whitney U test. The logistic multifactor regression method was used to analyze the risk factors of children’s early prognosis. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**Clinical and Laboratory Observations**

The age of the patients on admission ranged from 1 day to 14 years old, and the median age was 25 months. More than 60% of the patients were younger than 3 years old. There were 114 male and 113 female patients, and the gender ratio was close to 1:1. Of the 227 cases, 113 (49.8%) were diagnosed as an infection-associated hemophagocytic syndrome. Epstein-Barr virus (EBV) was the most common pathogen, accounting for 46.6% (73/158). Other pathogens included *Cytomegalovirus* (CMV), *Rickettsia tsutsugamushi*, *Mycobacterium tuberculosis*, *Leishmania donovani*, *Plasmodium*, *Escherichia coli*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, etc. Other potential triggering factors of HLH are as follows: 3 cases associated with juvenile idiopathic arthritis, 3 cases associated with systemic lupus erythematosus, 1 case associated with malignant lymphoma, 2 cases associated with acute lymphoblastic leukemia, 1 case associated with Langerhans-cell histiocytosis, and 1 case associated with Chediak Higashi syndrome. Twenty-nine (12.8%) patients underwent gene testing with the consent of their guardians, 16 of them had PRF1 gene mutation. Among the 16 children with PRF1 exon mutations, the ratio of male to female was 1:0.6, the youngest was 1 month old, and the oldest was 4 years old. After treatment, 93.8% (15/16) of these children improved and were discharged. The 3 main clinical manifestations were fever (98.7%), hepatomegaly (95.6%), and splenomegaly (92.1%). The clinical manifestations observed in the patients are shown in Figure 1.

The 3 main laboratory abnormalities were HDL-C decrease (99.1%), the presence of bone marrow hemophagocytosis (88.7%), and CRP increase (88.5%). The abnormal laboratory test results observed in the patients in Table 1. Among the children with nervous system symptoms, 5 cases received head magnetic resonance imaging examinations, of which 4 cases were normal, and the lateral ventricles were widened in 1 patient. Four cases received cerebrospinal fluid examination, and the white blood cells count in cerebrospinal fluid were increased (36-126) ×10^3/L.

**Prognostic Factors Analysis**

The non-survivors had a younger age and higher incidence of severe serous effusion, lower levels of albumin, platelet, hemoglobin, fibrinogen, sodium, HDL-C, low-density lipoprotein cholesterol, and total cholesterol, and higher levels of CRP and LDH. APTT, prothrombin time, and thrombin time in the nonsurvivor group were also significantly prolonged (\( P < 0.05 \), respectively). Detailed data between survivors and nonsurvivors are listed in Table 1.

Receiver operating characteristic curve was constructed for the continuous variable indexes with \( P \)-value < 0.05 in Table 1, and the corresponding tangent point of their maximum Yoden index was taken as the reference value, and the continuous variables were converted into binary variables for logistic regression analysis. Among the clinical characteristics and laboratory features analyzed, albumin < 25 g/L, APTT > 65 s, and LDH > 1000 U/L were independent risk factors for poor prognosis in children with hemophagocytic syndrome, and odds ratio values were 2.515, 3.094, and 2.378, respectively, while age > 28 months was a protective factor (\( P < 0.05 \), respectively) (Table 2).

**Treatment and Outcome**

Children admitted before 2008 received the 1994 regimen, and children admitted after 2008 received the 2004 regimen. 65 patients (28.63%) were treated according to the HLH-1994 or HLH-2004 regimen, 451 patients received
anti-infection plus high-dose IVIG and/or glucocorticoid and other forms of supportive treatment, 17 patients were treated with supportive therapy such as high-dose IVIG and/or glucocorticoids, and the remaining 25 patients were only treated with anti-infective therapy. Of the 227 children, 67 (29.52%) died within 30 days of onset. Among the 67 non-survivors, 32 cases were considered as infection-related HLH, including 6 cases of EBV-related HLH, 7 cases of FIGURE 2. Abnormal laboratory findings in the children with hemophagocytic lymphohistiocytosis. CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol.

FIGURE 2. Abnormal laboratory findings in the children with hemophagocytic lymphohistiocytosis. CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol.

| TABLE 1. Clinical Characteristics and Laboratory Features Between Hospital Survivors and Nonsurvivors Groups |
|---------------------------------------------------------------|
| Clinical Characteristics and Laboratory Features | Survivors (n = 160) | Nonsurvivors (n = 67) | Z/χ²/t | P |
|---------------------------------------------------------------|
| Age (mo)* | 29.5 (13.0, 62.5) | 17.0 (10.0, 39.0) | −2.489 | 0.013 |
| Sex, n (%) | 75 (46.9) | 39 (58.2) | 2.427 | 0.146 |
| Treatment (by hemophagocytic lymphohistiocytosis-1994/2004 regimen), n (%) | 44 (27.5) | 21 (31.3) | 0.341 | 0.630 |
| Serous cavity effusion, n (%) | 78 (48.8) | 45 (67.2) | 6.450 | 0.013 |
| Splenomegaly, n (%) | 149 (93.1) | 60 (89.6) | 0.862 | 0.582 |
| Enlarged lymph nodes, n (%) | 100 (62.5) | 35 (52.2) | 2.063 | 0.182 |
| Hepatomegaly, n (%) | 153 (95.6) | 65 (97.0) | − | 1.000 |
| Albumin (g/L) | 28.7 ± 5.7 | 23.9 ± 5.4 | 5.893 | 0.000 |
| Serum potassium (mmol/L) | 4.0 ± 0.7 | 4.1 ± 0.8 | −1.043 | 0.298 |
| Days from admission to diagnosis* | 3 (2, 5) | 3 (2, 5) | −1.892 | 0.065 |
| Days (from onset to admission)* | 7 (5, 10) | 7 (4, 10) | −0.846 | 0.399 |
| Total days of fever* | 12.0 (8.2, 17.0) | 11.0 (8.0, 16.0) | −1.052 | 0.294 |
| Leukocyte (>10⁹/L)* | 0.825 (0.459, 3.328) | 0.775 (0.473, 1.400) | −0.993 | 0.322 |
| Platelet (<10⁹/µL)* | 59 (39, 81) | 45 (30, 63) | −3.244 | 0.001 |
| Hemoglobin (g/L)* | 88 (79, 102) | 85.0 (73, 90) | −2.685 | 0.007 |
| Ferritin (µg/mL)* | 1461.0 (638.5, 1500) | 920.7 (1500, 1500) | −1.572 | 0.116 |
| Fibrinogen (g/L)* | 1.58 (1.15, 2.33) | 1.28 (0.83, 1.70) | −3.449 | 0.001 |
| Triglycerides (mmol/L)* | 2.95 (1.99, 4.13) | 3.05 (2.35, 3.93) | −0.419 | 0.677 |
| The proportion of NK cells (%)* | 4.87 (2.92, 7.40) | 6.36 (2.78, 13.20) | −1.694 | 0.090 |
| Alanine aminotransferase (U/L)* | 119 (59, 241) | 114 (73, 260) | −0.681 | 0.497 |
| Serum urea (µmol/L)* | 3.53 (2.60, 4.68) | 4.19 (2.63, 8.10) | −1.730 | 0.084 |
| Serum creatinine (µmol/L)* | 33.0 (25.5, 42.7) | 37.6 (30.0, 58.8) | −1.398 | 0.163 |
| Serum sodium (µmol/L)* | 133.0 (130.9, 135.3) | 131.0 (128.7, 134.2) | −2.739 | 0.006 |
| C-reactive protein (µg/mL)* | 30.3 (12.0, 65.6) | 56.0 (17.2, 113.0) | −2.676 | 0.007 |
| High-density lipoprotein cholesterol decreased (<1.04 mmol/L, n %) | 157 (98.1) | 67 (100) | − | 0.557 |
| Low-density lipoprotein cholesterol increases (>3.10 mmol/L, n %) | 6 (3.8) | 2 (3.0) | − | 1.000 |
| Total cholesterol (>5.20 mmol/L, n %) | 9 (5.6) | 2 (3.0) | − | 0.514 |
| Lactose dehydrogenase (U/L)* | 729 (490, 1764) | 1523 (584, 2541) | −3.584 | 0.000 |
| Activated partial thromboplastin time (s)* | 47.8 (40.1, 55.8) | 58.4 (45.4, 82.5) | −4.547 | 0.000 |
| Prothrombin time (s)* | 14.9 (13.4, 16.8) | 17.0 (14.6, 22.7) | −4.428 | 0.000 |
| Thrombin time (s)* | 19.7 (17.5, 25.8) | 24.2 (18.8, 42.8) | −3.759 | 0.000 |

*Median (interquartile range).
▲Fisher exact test
NK indicates natural killer.
CMV-related HLH, and 5 cases of EBV and CMV coinfection-related HLH. Among the 35 cases of non-infection-related HLH, there was 1 case of malignant lymphoma, 1 case of systemic lupus erythematosus, 1 case of acute lymphoblastic leukemia, 2 cases of PRFI mutation, and 1 case of HLH family history. Of the 65 patients who received the HLH-1994 or HLH-2004 regimen, 44 cases (67.7%) achieved remission.

Of the 113 infection-associated hemophagocytic syndromes, 38 (33.6%) were treated with HLH-1994 or HLH-2004 regimen,\(^4,5\) 42 (37.2%) were treated with anti-infection therapy according to etiologic examination or experience. Six cases with \(R.\) tsutsugamushi-related HLH were treated with azithromycin and/or chloramphenicol, 2 cases with \(L.\) donovani associated HLH were treated with antimonials, and 1 case with malaria-related HLH was treated with chloroquine phosphate. These hemophagocytic syndrome associated with special pathogenic infection have obtained satisfactory curative effects after anti-infection treatment. Seventeen (23.29%) cases of EBV-related HLH cases died.

The mortality rate in 2013 to 2018 was significantly lower than that in 2001 to 2012 (16.35% vs. 40.65%, \(P = 0.000\)). Our study found that compared with the period from 2001 to 2012, the time from onset to admission and the time from admission to definitive diagnosis of HLH children in the period from 2013 to 2018 were significantly reduced (\(P < 0.05\), respectively) (Table 3).

### DISCUSSION

HLH is a rare immune-mediated life-threatening disease, which was first reported in children in 1952.\(^6\) HLH has complex etiology, changeable and nonspecific clinical symptoms, rapid progress, difficult treatment, and high mortality. Due to the differences in race, genetic and environmental factors, EBV infection rates, and so on, the incidence rate of children with hemophagocytic syndrome varies in different countries and regions. According to a previous study, the annual incidence rate of HLH in Japan was 1/800,000 in the early part of this century, more than half of them were children younger than 15 years old.\(^7\) In our study, due to limited conditions, we only detected PRFI gene mutation. According to previous reports, ~20% to 40% of prime HLH cases harbor a PRFI mutation, which encodes for the perforin protein.

Generally, the clinical symptoms and signs of HLH are nonspecific, including persistent fever, hepatosplenomegaly, edema, rash, and pale complexion. In our study, there were >10 kinds of clinical symptoms and signs, of which only the incidence of fever and hepatosplenomegaly were present in >90% of cases, and most of the other symptoms and signs were observed in <20%. These clinical symptoms are changeable and nonspecific, which poses a severe challenge to the early diagnosis of clinicians. It is worth noting that previous reports have observed that the incidence of fever in children with HLH is 100%.\(^8,9\) Our study shows that although fever was very common in children with HLH, it was not present in 100% of the cases.

Due to the involvement of various systems, HLH can have a variety of laboratory test abnormalities. Cytopenias, hyperferritinemia, high lactate dehydrogenase, elevated serum transaminases, and hemophagocytosis in bone marrow were the most common laboratory abnormalities.\(^5,10\) Our study found that the increase of CRP is common, which indicates that there is an obvious inflammatory reaction in HLH children. It has also been reported that CRP level in

### TABLE 2. Logistic Regression Analysis of Prognostic Factors of Hemophagocytic Lymphohistiocytosis

| Risk Factors | \(B\) | SE | Wald | Exp (\(B\)) | Lower | Upper | \(P\) |
|--------------|-------|----|------|-------------|-------|-------|------|
| Age (> 28 mo) (mo) | −1.222 | 0.397 | 9.457 | 0.295 | 0.135 | 0.642 | 0.002 |
| Hemoglobin (< 90 g/L) | −0.044 | 0.392 | 0.012 | 0.957 | 0.444 | 2.064 | 0.912 |
| Platelet (< 50×10^9/L) | 0.390 | 0.332 | 1.380 | 1.478 | 0.770 | 2.834 | 0.240 |
| Serum sodium (< 130 mmol/L) | −0.336 | 0.449 | 0.558 | 0.715 | 0.296 | 1.725 | 0.455 |
| Albumin (< 25 g/L) | 0.922 | 0.383 | 5.810 | 2.515 | 1.188 | 5.323 | 0.016 |
| Activated partial thromboplastin time (> 65 s) | 1.129 | 0.485 | 5.418 | 3.094 | 1.195 | 8.008 | 0.020 |
| Prothrombin time (> 16 s) | 0.605 | 0.426 | 2.023 | 1.832 | 0.796 | 4.218 | 0.155 |
| Fibrinogen (< 1.4 g/L) | −0.320 | 0.433 | 0.546 | 0.726 | 0.311 | 1.696 | 0.460 |
| C-reactive protein (> 55 mg/L) | 0.474 | 0.370 | 1.643 | 1.606 | 0.778 | 3.317 | 0.200 |
| Lactate dehydrogenase (> 1000 U/L) | 0.866 | 0.383 | 5.106 | 2.378 | 1.122 | 5.042 | 0.024 |
| Thrombin time (> 28 s) | 0.102 | 0.507 | 0.041 | 1.108 | 0.410 | 2.992 | 0.840 |
| Serum cavity effusion | 0.192 | 0.384 | 0.251 | 1.212 | 0.571 | 2.571 | 0.616 |

### TABLE 3. Comparison of Mortality in Different Periods

| Different Periods | Death Within 30 Days, n (%) | Time From Onset to Admission, Median (Interquartile Range) (d) | Time From Admission to Definite Diagnosis, Median (Interquartile Range) (d) | Treatment (by Hemophagocytic Lymphohistiocytosis-1994/2004 Regimen), n (%) |
|-------------------|-----------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 2013-2018         | 17 (16.35)                  | 6.0 (4.0, 8.75)                                               | 3.0 (2.0, 4.0)                                                           | 29 (27.88)                                                               |
| 2001-2012         | 50 (40.65)                  | 7.0 (5.0, 11.0)                                              | 4.0 (2.0, 6.0)                                                           | 36 (29.27)                                                               |
| \(\chi^2/Z\)     | 16.001                      | −2.517                                                       | −2.620                                                                  | 0.053                                                                    |
| \(P\)             | 0.000                       | 0.012                                                        | 0.009                                                                    | 0.883                                                                    |
children with secondary HLH is significantly higher than that in children with primary HLH. For HLH patients with underlying autoimmune diseases, higher CRP means a higher risk of death. Our study shows that CRP in the nonsurvival group is significantly higher than that in the survival group, but it is not an independent risk factor for poor prognosis by the logistic regression analysis.

It should be noted that the most common laboratory abnormality found in our study was the decrease of HDL-C, which seemed to have never been mentioned in previous studies. Although hypertriglyceridemia is one of the diagnostic criteria for HLH, the incidence of hypertriglyceridemia was only 51.3% in our study, while the incidence of decreased HDL-C was >99%. Therefore, it is worth discussing whether HDL-C can be considered to replace hypertriglyceridemia as one of the diagnostic criteria for HLH.

One hundred twenty-three children had serous effusions, which were caused by hypoalbuminemia. The incidence of serous exudation in the survival group was lower than that in the nonsurvival group ($P = 0.013$). Similarly, the plasma albumin level in the survival group was significantly higher than that in the nonsurvival group ($P = 0.000$). Logistic regression analysis showed that serous exudation was not an independent risk factor for the prognosis of HLH. It is well known that hypoalbuminemia can cause serous exudation, so we believe that hypoalbuminemia plays an important role in the prognosis of HLH in children.

Different studies have different independent risk factors for the prognosis of children with HLH, due to different sample sizes, study outcome definitions and research projects, etc. According to previous studies, poor prognosis in children with HLH was associated with younger age (<2 y), hypalbuminemia, high lactate dehydrogenase, thrombocytopenia, hyperbilirubinemia, persistent fever (>2 wk) and prolonged APTT. etc. Albumin <25 g/L, prolonged APTT (>65 s), and high lactate dehydrogenase (>1000 U/L) were the most common independent risk factors at diagnosis in our study. In our study, age >28 months at diagnosis was an independent protective factor. In other words, the smaller the age at diagnosis (<28 mo) the higher the risk of death within 30 days. The decrease in albumin and the prolongation of APTT are often considered to be related to liver function impairment in children with HLH. Therefore, the protection of liver function in children with HLH may play a positive role in improving the prognosis.

HLH is a life-threatening syndrome for children. In our study, nearly 30% of children died within 30 days after the onset of the disease. Other studies have reported a lower mortality rate in children with HLH, ranging from 13.8% to 28.1%. Looking at our data, the mortality of HLH in children mainly occurred in the early stage, and the mortality rate in the past 6 years has dropped significantly to 16.35%. This proves that with the deepening of doctors’ understanding of HLH which is a fatal disease in children, the mortality rate can be significantly decreased. In our study, about two thirds of children receiving standard HLH-1994 or HLH-2004 protocol achieved effective remission. The appearance of HLH-1994 or HLH-2004 protocol has greatly improved the prognosis of patients with HLH. However, a study by Japanese scholars found that outcomes in children with HLH who were treated with the same protocol were different among HLH subtypes. The 2004-HLH regimen has a significant therapeutic effect in children with EBV-associated HLH. A small sample single-center study found that 16 of 24 children with secondary HLH who had not received the 2004-HLH regimen had a good early outcome and no one died within 30 days after diagnosis. According to our data, there was no difference in the rate of HLH treatment between the survivors and nonsurvivors. This may be related to the fact that there are many patients who do not need to receive an HLH regimen.

Compared with 2001 to 2012, our study found that the mortality within 30 days of diagnosis of HLH in children from 2013 to 2018 has decreased significantly, while the time from onset to admission and the time from admission to definitive diagnosis has been shortened as well, during the same period. This suggests that for children with HLH, early diagnosis and timely treatment may be of great significance to improve their short-term prognosis.

In summary, due to the wide heterogeneity of etiology, diverse and atypical clinical manifestations, and rapid progress of the disease, it is difficult to distinguish HLH from other underlying disease, and it is easy to delay the diagnosis and treatment, hence the mortality rate is high. Therefore, early diagnosis and timely treatment are very important for children suspected of HLH. The decrease of HDL-C is very common in children with HLH, which is helpful for early diagnosis. If albumin <25 g/L, APTT >65s, LDH >1000 U/L, or age <28 months at diagnosis in children with HLH, we should be alerted to the poor prognosis in the early stage, and therefore should be treated as soon as possible to improve the prognosis of children. There are different subtypes of HLH, and the efficacy of the 2004-HLH regimen in children with different subtypes of HLH is not the same. Appropriate treatment strategies should be developed for each subtype. Early identification of risk factors for HLH and timely diagnosis and treatment are important measures to improve the prognosis of HLH in children.

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