Risk factors of early death in adult patients with secondary hemophagocytic lymphohistiocytosis: a single-institution study of 171 Chinese patients

Yanchun Zhao, Danlei Lu, Shanshan Ma, Li Li, Jingjing Zhu, De Zhou, Yanlong Zheng, Xiudi Yang, Lixia Zhu, Mingyu Zhu, Mixue Xie, Jianai Sun, Xiujin Ye and Wanzhuo Xie

Department of Hematology, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, People’s Republic of China

ABSTRACT

Background: Adult secondary hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening syndrome characterized by excessive activation of mononuclear-phagocytic system resulting in hyperinflammatory response. To date, the factors influencing early death of HLH are still not fully elucidated.

Patients and Methods: We did a retrospective study of 171 adult patients with newly diagnosed HLH at our institution from January 2012 to April 2018. All patients’ clinical features, laboratory findings, treatments and prognosis were reviewed.

Results: The median age was 49 years (range, 18–88 years), and 110 (64.3%) were male. The major underlying trigger of HLH was malignancy (88/171, 51.5%), especially non-Hodgkin lymphoma. In a multivariate analysis, age ≥ 54 years (P = 0.002), platelet ≤ 39.5 × 10^9/L (P = 0.028), activated partial thromboplastin time (APTT) ≥ 54 sec (P = 0.048), triglyceride ≥ 3.23 mmol/L (P < 0.001), lactate dehydrogenase (LDH) ≥ 1300 U/L (P = 0.012) and malignancy (P = 0.001) were significantly associated with early death in HLH. Then, patients were classified into four groups according to the number of risk factors at the time of diagnosis: low risk (zero, one or two risk factors), low intermediate risk (three risk factors), high intermediate risk (four risk factors) and high risk (at least five risk factors), with the 30-day overall survival (OS) of 92.4%, 58.8%, 30.0% and 4.8%, respectively (P < 0.001).

Conclusions: Patients with old age, thrombocytopenia, prolonged APTT, hypertriglyceridemia, elevated LDH and malignancy had inferior survival. It is important to identify those patients at risk of early death, which may guide treatment and reduce mortality.

Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome (HPS), is considered to be a life-threatening disease characterized by cytotoxic T lymphocyte (CTL) and natural killer (NK) cell dysfunction resulting in excessive activation of macrophages and a large number of inflammatory cytokines hypersecretion. This syndrome was first described as ‘histiocytic medullary reticulosis’ by Scott and Robb-Smith in 1939 [1]. The common manifestations of HLH are fever, hepatosplenomegaly, pancytopenia, hypertriglyceridermia, hypofibrinogenemia, hyperferritinemia and hemophagocytosis in bone marrow, spleen or lymph nodes [2].

HLH can be divided into two types: primary (hereditary) and secondary (reactive). The primary form is further differentiated as familial HLH which is presented as a family history or identifiable gene defects such as PRF1 [3], UNC13D [4], STX11 [5] and STXBP2 [6], and immune deficiency associated HLH including Chédiak-Higashi syndrome (CHS), Griscelli syndrome (GS) and X-linked lymphoproliferative syndrome (XLP) [7]. Secondary HLH without underlying genetic abnormalities are mostly triggered by infections, autoimmune diseases and malignancies.

In the past, HLH was thought of primarily as a pediatric disease and most diagnostic guidelines, international databases and treatment trials in HLH were based on pediatric populations [8]. Indeed, HLH can occur at any age, of which adults comprise approximately 40% of cases [9]. Adult HLH has a progressive course with the mortality rate ranging from 8% in macrophage activation syndrome (MAS) [10] to 20%–60% in malignancy-associated HLH (M-HLH) [9,11,12]. In fatal HLH, death usually occurs during the first 4–8 weeks due to multiple organ failure, bleeding or sepsis [12]. Currently, a series of studies have reported prognostic factors for long-term survival in HLH [13–15]. However, the factors influencing its early death are not completely elucidated.

Herein, we did a retrospective study of 171 adult patients with secondary HLH diagnosed consecutively in our institution and aimed to determine possible risk factors related to early death in HLH.
Patients and methods

Patients selection

We retrospectively analyzed a cohort of 171 adult patients (age ≥18 years) with newly diagnosed HLH in our institution from January 2012 to April 2018. The diagnosis of HLH was based on the HLH-2004 criteria from the Histiocyte Society [2]. All the patients included in this study are required to meet at least five of the following criteria: (1) prolonged fever (a temperature ≥38.5 °C for ≥7 days), (2) splenomegaly (the costal margin exceeded 3 cm), (3) cytopenia involving in at least two lineages of peripheral blood (neutrophil count <1.0 × 10^9/L, hemoglobin <90 g/L or platelet <100 × 10^9/L), (4) hypertriglyceridemia (fasting triglycerides ≥3 mmol/L) and/or hypo- fibrinogenemia (fibrinogen ≤1.5 g/L), (5) hemophagocytosis in bone marrow, spleen or lymph nodes, (6) low or absent NK cells activity, (7) serum ferritin ≥500 μg/L and (8) soluble CD25 (soluble interleukin-2 receptor) ≥2400 IU/ml.

However, the tests for soluble CD25 levels and NK cell activity were not available in our institution, so diagnosis was done when five out of the other six criteria fulfilled. According to the guidelines based on the tenets of the revised Helsinki protocol, written informed consents were obtained from all patients.

Data collection

The following regular laboratory findings were collected: neutrophil (Neu), lymphocyte (Lym), hemoglobin (Hb), platelet, fibrinogen (Fib), activated partial thromboplastin time (APTT), prothrombin time (PT), D-Dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, globulin, total cholesterol (TC), triglyceride (TG), lactate dehydrogenase (LDH), alkaline phosphatase (AKP), total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IB), γ-glutamyl transpeptidase (γ-GT), ferritin and sodium. Patients’ clinical characteristics, treatments and prognosis were also used for analysis. Follow-up was performed by making phone calls or reviewing medical records. Early death was defined as death within 30 days after diagnosis.

Statistical analysis

Continuous variables are presented as median with interquartile range (IQR). Categorical variables are shown as frequencies and percentages (n, %). Due to abnormal distribution, continuous variables between survivors and non-survivors were compared by Mann-Whitney U-tests. The Pearson’s Chi-square test was used for categorical variables of survivors and non-survivors. The Kaplan-Meier method with the log-rank test was used for survival curves. Univariate and multivariate analysis were performed according to the Cox proportional hazard model. A two-side P-value < 0.05 was considered statistically significant. All statistical calculations were processed using the statistical software package SPSS 22.0 (SPSS, U.S.A).

Results

Patient characteristics

A total of 171 adult patients with HLH [110 males, 61 females; median age, 49 years (range, 18–88 years)] were selected in this study. All patients presented prolonged high fever. Other common clinical manifestations included splenomegaly (85.4%), lymphadenopathy (63.2%) and hepatomegaly (40.9%). Laboratory abnormalities included neutropenia (34.5%), anemia (57.3%), thrombocytopenia (91.2%), hypofibrinogenemia (62.0%), hypertriglyceridemia (36.3%), hyperferritinaemia (96.5%) and hemophagocytosis in the bone marrow (88.9%). The underlying triggers in HLH patients were distributed as follows: malignancies (51.5%), followed by infections (26.3%), autoimmune disorders (4.1%) and unknown triggers (18.1%). In malignancy-associated cases, hematological diseases were dominant, especially non-Hodgkin lymphomas. All treatment regimens were decided according to the guideline of the HLH-1994/HLH-2004 treatment protocol. Patients received therapies consisting of corticosteroids, immunosuppressive drugs or intravenous immunoglobulin (IVIG), of which 43.8% of patients received corticosteroid and etoposide (VP-16).

Comparison of patients’ clinical and laboratory findings between survivors and non-survivors

In our study, sixty-one patients died during the first 30 days after diagnosis and the 30-day mortality was 35.7%. Comparisons of clinical and laboratory parameters between survivors and non-survivors were shown in Table 1. Non-survivors were older (P = 0.015). APTT and PT were more prolonged in non-survivors than in survivors (P = 0.022 and P < 0.001, respectively). The levels of AST, AKP and LDH were higher in non-survivors (P = 0.046, P = 0.006 and P = 0.002, respectively). The indicators reflecting jaundice such as TB, DB and IB were more serious in non-survivors (P = 0.001, P < 0.001 and P = 0.001, respectively). However, there were three parameters significantly decreased in non-survivors: lymphocyte (P < 0.001), platelet (P < 0.001) and fibrinogen (P = 0.002). Furthermore, M-HLH was more common in non-survivors (P < 0.001).

Univariate analysis for risk factors

Table 2 displays the results of univariate analysis for the potential predictors of HLH patients’ early death.
The 30-day mortality was associated with age ≥54 years (P = 0.008), Neu ≤1.95 × 10⁹/L (P = 0.041), Lym ≤0.37 × 10⁹/L (P = 0.003), platelet ≤39.5 × 10⁹/L (P < 0.001), fibrinogen ≤1.02 g/L (P < 0.001), APTT ≥54 sec (P = 0.009), PT ≥16.5 sec (P < 0.001), triglyceride ≥3.23 mmol/L (P < 0.001), LDH ≥1300 U/L (P < 0.001), ferritin ≥13,000 ng/ml (P = 0.006), AKP ≥233.5 U/L (P = 0.001), TB ≥42 µmol/L (P = 0.001), DB ≥11.5 µmol/L (P = 0.001), IB ≥14 µmol/L (P = 0.004), γ-GT ≥89 U/L (P = 0.009), sodium ≥132 mmol/L (P = 0.042) and malignancy (P < 0.001). No significantly different was found in the other parameters for early death.

### Multivariate analysis

To determine independent predictors of HLH patients’ early death, the forward conditional Cox region model was performed for the 17 significant variables identified by univariate analysis. Subsequently, only age ≥54 years [HR = 2.34, 95% Confidence interval (CI) 1.37–3.98, P = 0.002], platelet ≤39.5 × 10⁹/L [HR = 2.36, 95% CI (1.10–5.06), P = 0.028], APTT ≥54 sec [HR = 1.70, 95% CI (1.00–2.87), P = 0.048], triglyceride ≥3.23 mmol/L [HR = 2.89, 95% CI (1.71–4.88), P < 0.001], LDH ≥1300 U/L [HR = 1.97, 95% CI (1.16–3.32), P = 0.012] and malignancy [HR = 3.21, 95% CI (1.63–6.30), P = 0.001] were statistically significant (Table 3). In addition, Figure 1 describes survival curve of HLH patients with different risk factors in 30 days after diagnosis using Kaplan-Meier method.

Risk groups were defined by comparing the relative risk of early death in patients with each possible number of risk factors (0, 1, 2, 3, 4, 5 or 6).
Interestingly, there was no statistical significance in 30-day survival between patients with zero and one risk factor ($P = 0.915$). The same was true between one and two risk factors ($P = 0.563$), and between five and six risk factors ($P = 0.461$). Then, we combined categories with similar relative risks (e.g. 0, 1 with 2 or 5 with 6) and classified patients into four groups: low risk (zero to two risk factors; 79/171), low intermediate risk (three risk factors; 51/171), high intermediate risk (four risk factors; 20/171) and high risk (at least five risk factors; 21/171), with the 30-day overall survival (OS) of 92.4%, 58.8%, 30.0% and 4.8%, respectively ($P < 0.001$) (Figure 2). Compared with the patients in low risk group, patients in high risk, high intermediate risk and low intermediate risk group have a 31-fold, 14-fold and 7-fold increase in risk of early death, respectively [HR = 30.75, 95% CI (11.67–81.06), $P < 0.001$; HR = 14.10, 95% CI (5.34–37.23), $P < 0.001$ and HR = 6.52; 95% CI (2.63–16.17), $P < 0.001$].

**Figure 2.** The survival curve and overall survival (OS) of four risk groups by 30 days after diagnosis. Low risk group (zero, one or two risk factors), low intermediate risk group (three risk factors), high intermediate risk group (four risk factors) and high risk group (at least five risk factors).

**Discussion**

As is well known that adult HLH has a poor prognosis with high mortality. Although the discoveries in recent decades have produced extraordinary advances in our understanding of HLH, early death remains a major challenge in the treatment of HLH, which warrants the need for determining its risk factors to

### Table 3. Multivariate analysis of risk factors for early death in HLH.

| Risk factors | Hazard ratio | 95% Confidence interval | $P$-value |
|--------------|--------------|-------------------------|-----------|
| Age ≥54 years | 2.34         | 1.37–3.98               | 0.002*    |
| Platelet ≤39.5 × 10^9/L | 2.36 | 1.10–5.06 | 0.028* |
| APTT ≥54 sec | 1.70         | 1.00–2.87               | 0.048*    |
| Triglyceride ≥3.23 mmol/L | 2.89 | 1.71–4.88 | <0.001* |
| LDH ≥1300 U/L | 1.97         | 1.16–3.32               | 0.012*    |
| Malignancy    | 3.21         | 1.63–6.30               | 0.001*    |

Abbreviations: APTT: activated partial thromboplastin time, LDH: lactate dehydrogenase.

*Significantly different.
improve patients’ outcomes. Thus, we reviewed clinical and laboratory findings of HLH patients and found that malignancy, platelet, age, LDH, APTT and triglyceride were independent risk factors of early death.

In this study, the most common trigger of HLH was malignancy (51.5%), which was similar with the outcomes of four studies conducted by Riviere et al. [12], Parikh et al. [16], Schram et al. [17] and Buyse et al. [18], respectively. However, this may conflict with other reported literature as infections were the leading trigger of HLH [14]. Interestingly, lymphoma-associated HLH was reported more frequent in Asian populations than Western populations [19,20], that is to say, genetic and environmental factors may impact its development. M-HLH is characterized by the release of several cytokines, such as interferon-γ (IFN-γ), interleukin-10 (IL-10) and IL-6, which are triggered due to the excessive secretion of proinflammatory cytokines and persistent antigen stimulation by the tumor cells. These cytokines are associated with the typical clinical features and laboratory findings commonly observed in HLH patients, including prolonged fever, liver damage, hyperferritinemia and splenomegaly. Furthermore, the immune disorder influenced by tumor microenvironment will further promote the development of M-HLH. In addition, M-HLH may also occur during chemotherapy. The loss of immune homeostasis induced by chemotherapy aggravates T-cell dysfunction, which may lead to infections in these patients. So far, accumulating evidence indicated that patients with M-HLH had a worse prognosis compared with those with non-M-HLH [12,14,16,17].

Thrombocytopenia was considered as a consistent prognostic factor in HLH [13,21–24]. Similarly, our results also found that platelet less than 39.5 × 10^9/L was an independent risk factor of 30-day survival. There are several mechanisms probably resulting in thrombocytopenia, including production decreased due to bone marrow failure or excessive consumption caused by disseminated intravascular coagulopathy (DIC) and hypersplenism. Severe thrombocytopenia is related to severe internal bleeding especially in the brain, which is often fatal. Currently, there is substantial evidence supporting the link between platelet and inflammation. The platelet expresses Toll-like receptors (TLRs), indicating a capacity to directly engage microbial pathogens similar to leukocytes [25]. In addition, the platelet adheres to von Willebrand factor (VWF) bound to endothelial cells, eliciting gathering and rolling of leukocytes on the endothelial surface [26]. Besides, platelet has a reciprocal relationship with the complement system, aiding in the clearance of an infection [27,28]. Moreover, platelet reflects the function and reserve of bone marrow, that is to say, thrombocytopenia may partly indicated bone marrow failure. All in all, thrombocytopenia leads to an increase in the risk of bleeding, damages the immune response and reflects the bone marrow failure, suggesting a poor prognosis in patients with HLH.

Additionally, age is also an independent prognostic factor. Elderly patients had shorter survival time, in consonance with the results of other studies [13,29]. It may be due to senescent organs resulting in more severe organ dysfunction [24] or other comorbid illnesses affecting the outcomes of HLH. Hyperbilirubinemia was a predictor of death [15]. Our results described that serum bilirubin levels were high in non-survivors. Coagulopathy was frequently seen in HLH, and its cause is multifactorial, owing to thrombocytopenia, liver injury, impairment in synthetic function of coagulation factors or DIC [30]. Li et al. [22] analyzed 85 adult HLH patients and found that the levels of fibrinogen in the dead group were significantly lower than those of the patients in the survival group. In our cohort, 62.0% of patients had low fibrinogen level. In addition, hypofibrinogenemia was significantly different between survivors and non-survivors. A retrospective study of 205 adult HLH patients indicated that PT prolonged >3s was correlated with poor survival [23], so were our results. In multivariate analysis, prolonged APTT was an independent risk factor of poor survival in adult patients, accordance with the result from a study based on 89 pediatric HLH patients [31]. APTT provides a useful qualitative assessment for anticoagulation activity and is a risk factor for bleeding events in patients. Triglycerides may not be increased until the liver has been impaired for a period of time; in other words, hypertriglyceridemia is a sign of severe liver impairment. There was a statistically significance for increased triglycerides as a predictor of adverse outcome in our study. LDH is a glycolytic enzyme, which turns the sugar into energy in cells. This enzyme is widely present in many kinds of organs and tissues, especially in rapidly growing tumors. Therefore, serum LDH is often regarded as an index of organ injury and tumor burden. Prolonged APTT, hypertriglyceridemia and elevated LDH were all related to liver function damage, which revealed that HLH patients with early death more frequently suffered severe liver dysfunction. To some extent, abnormal liver function aggravates the development of HLH and affects its prognosis.

However, several other factors have also been regarded as significant indicators to the outcomes. Ferritin, a valuable diagnostic and prognostic marker in HLH, has been previously reported that its level greater than 10,000 µg/L have 90% sensitive and 96% specific in pediatric HLH [32]. Although almost all adults with HLH meet the diagnostic criterion of serum ferritin greater than 500 µg/L, the sensitivity and specificity of this marker in the adult population is much less impressive [33]. A review showed that a marked hyperferritinemia over 50,000 mg/L was not
seen most often in adult HLH patients, but in patients with renal failure, hepatocellular injury, infections and hematological malignancies [34]. Recent data had reported that hyperferritinemia was also an independent prognostic variable of mortality in HLH patients [13,14]. In our study, we found a significant correlation between hyperferritinemia and 30-day OS in univariate, but not multivariate analysis. Notably, the low percentage of glycosylated ferritin was reported to be more sensitive and specific than ferritin to identify patients at high risk of early death [35].

Hypoalbuminemia is generally considered as an indicator of malnutrition. Previous studies have found that hypoalbuminemia was related to the inferior outcomes in HLH [16,36–38]. However, there is no relationship between the albumin level and patient survival among our cohort. Perhaps the differences are due to the sample’s proportion of underlying diseases.

Hypercytokinemia was identified relatively early in the understanding of HLH pathophysiology [30], which is a major pathological feature of HLH. T-helper cell type 1 (Th1) and 2 (Th2) cytokines include IL-2, IL-4, IL-6, IL-10, IFN-γ and tumor necrosis factor (TNF)-α. Tang et al. [38,39] have demonstrated that a specific cytokine pattern could be used to diagnosis HLH in pediatrics and increased IL-10 at diagnosis was an independent prognostic factor of early death in children HLH. As yet, little is known about the prognostic significance of cytokines in early death with adult HLH patients. A study showed that adult HLH patients had elevated IL-6, IL-10 and IFN-γ level [40]. In our work, not all patients determined Th1/Th2 cytokines due to the unavailability of routine cytokine analysis at the beginning of the study or not performed. However, through analysis the data of 78 patients who were detected cytokines, we found that the level of IL-6 and IL-10 are significantly elevated in non-survivors compared to survivors (P = 0.042 and P < 0.001, respectively) (data not shown). In future, a series of prospective studies are needed to explore the association between cytokines and early adverse outcomes in adult HLH.

Another important finding is that we established a prognostic model for early stage of HLH which may be critical to guide treatment and reduce mortality. According to the number of risk factors at the time of diagnosis, the patients were classified into four groups: low risk, low intermediate risk, high intermediate risk and high risk, which was significantly different in 30-day OS. Therefore, we propose that timely and effective treatment should be given to HLH patients with over two risk factors as soon as possible.

Our study has some limitations. Firstly, it was performed retrospectively, with the possibility of bias in the selection of study population. Secondly, adult HLH was diagnosed according to HLH-2004 criteria, which focused on pediatric populations and may be too strict for adults with secondary HLH. Thus, further multicenter and prospective researches are warranted to validate our prognostic model and find more meaningful clinical parameters to help diagnose adult HLH.

Conclusions

We analyzed a single-center’s experience and emphasized the prognostic value of increasing age (≥54 years), thrombocytopenia (≤39.5 × 10^9/L), prolonged APTT (≥54 sec), hypertriglyceridemia (≥2.33 mmol/L), elevated LDH (≥1300 U/L) and malignancy to predict the risk of early death in adult HLH patients. Furthermore, our study established a prognostic model to categorize HLH patients into high, high-intermediate, low-intermediate and low risk subgroups according to the number of prognostic factors at the time of diagnosis. These results may help guide clinicians to make better treatment decisions to patients who bear a substantial risk of fatal outcome.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by National Natural Science Foundation of China [grant number 81372256].

References

[1] Scott RB, Robb-Smith AH. Histiocytic medullary reticuloctyosis. Lancet. 1939;234:194–198.
[2] Henter JI, Horne A, Aicó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–131.
[3] Stepp SE, Dufourcq-Lagelouse R, Le Deist F, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999;286:1957–1959.
[4] Feldmann J, Callebaut I, Raposo G, et al. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). Cell. 2003;115:461–473.
[5] zur Stadt U, Schmidt S, Kasper B, et al. Linkage of familial hemophagocytic lymphohistiocytosis type 5 (FHL-5) to chromosome 6q24 and identification of mutations in syntxin11. Hum Mol Genet. 2005;14:461–473.
[6] zur Stadt U, Rohr J, Seifert W, et al. Familial hemophagocytic lymphohistiocytosis type 5 (FHL-5) is caused by mutations in Munc18-2 and impaired binding to syntxin11. Am J Hum Genet. 2009;85:482–492.
[7] Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012;63:233–246.
[8] Daver N, McClain K, Allen CE, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer. 2017;123:3229–3240.
[9] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet. 2014;383:1503–1516.
A comprehensive analysis of Lymphoma-associated haemophagocytic syndrome in a large French multicentre cohort detects some clues to improve prognosis. Br J Haematol. 2018;183:68–75.

Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. Annu Rev Pathol. 2018;13:27–49.

Dai AT, Luong VT, Nguyen TT, et al. Risk factors for early fatal outcomes among children with hemophagocytic lymphohistiocytosis (HLH): a single-institution case-series in Vietnam. Pediatr Hematol Oncol. 2014;31:271–281.

Standage SW, Filippovich AH. Hemophagocytic lymphohistiocytosis syndromes. Pediatr Crit Care Med. 2014;16:385–393.

Bhat NS, Oshrine B, An Talano J. Hemophagocytic lymphohistiocytosis in adults. Leuk Lymphoma. 2019;60:19–28.

Schram AM, Campigotto F, Mullally A, et al. Marked hyperferritinemia does not predict for HLH in the adult population. Blood. 2015;125:1548–1552.

Nabergoj M, Marinova M, Binotto G, et al. Diagnostic and prognostic value of low percentage of glycosylated ferritin in acquired hemophagocytic lymphohistiocytosis: A single-center study. Int J Lab Hematol. 2017;39:620–624.

Huang SC, Chen JS, Cheng CN, et al. Hypoalbuminaemia is an independent predictor for hemophagocytic lymphohistiocytosis in childhood Epstein-Barr virus-associated infectious mononucleosis. Eur J Haematol. 2012;89:417–422.

Bin Q, Gao JH, Luo JM. Prognostic factors of early outcome in pediatric hemophagocytic lymphohistiocytosis: an analysis of 116 cases. Ann Hematol. 2016;95:1411–1418.

Luo ZB, Chen YY, Xu XJ, et al. Prognostic factors of early death in children with hemophagocytic lymphohistiocytosis. Cytokine. 2017;97:80–85.

Tang Y, Xu X, Song H, et al. Early diagnostic and prognostic significance of a specific Th1/Th2 cytokine pattern in children with haemophagocytic syndrome. Br J Haematol. 2008;143:84–91.

Lorenz F, Klimkowska M, Pawlowicz E, et al. Clinical characteristics, therapy response, and outcome of 51 adult patients with hematological malignancy-associated hemophagocytic lymphohistiocytosis: a single institution experience. Leuk Lymphoma. 2018;59:1840–1850.