Hemophagocytic Lymphohistiocytosis

Clinical Analysis of 103 Adult Patients

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Abstract: To investigate the clinical features of adult patients with hemophagocytic lymphohistiocytosis (HLH) and to explore possible risk factors for death, we retrospectively reviewed the medical records of 103 adult HLH patients hospitalized from 1997 to 2012. We analyzed the underlying diseases, clinical characteristics, 1aboratory findings, outcomes, and prognostic factors. The most common cause of HLH was hematologic malignancies (n = 49), followed by infectious diseases (n = 24) and autoimmune disorders (n = 14); 24 cases were of unknown etiology. Eight patients had a combination of underlying diseases. HLH was clinically characterized by high fever (96.1%), splenomegaly (79.6%), hepatomegaly (65.0%), lymphadenopathy (53.4%), proteinuria (31.1%), skin rash (25.2%), gastrointestinal hemorrhage (14.6%), disseminated intravascular coagulation (13.6%), increased creatinine (7.8%), and central nervous system involvement (12.6%) including altered mental status (9.7%) and cranial hemorrhage (2.9%). Laboratory abnormalities included cytopenia (99.0%), serum ferritin >500 ug/L (98.4%), liver dysfunction (98.1%), hypertriglyceridemia (88.5%), hemophagocytosis in bone marrow smear (87.4%), and hypofibrinogenemia (60.9%).

In addition to the treatment they received for the underlying causes, patients received therapy for HLH consisting of corticosteroids, immunosuppressive drugs, and intravenous immunoglobulin. Twenty-six patients (25.2%) recovered after treatment, and 19 of them achieved long-term remission during follow-up. Seventy-seven patients (74.8%) died because of tumor, sepsis, multiple organ failure, or HLH-related organ hemorrhage and coagulopathy. The deceased patients were more likely to be older at disease onset, male, and to present with splenomegaly and thrombocytopenia, compared to the survivors. Treatment for the underlying diseases combined with corticosteroids, immunosuppressive agents, and immunoglobulin therapy may improve the prognosis of HLH. More attention should be paid to high-risk patients to prevent the development of serious complications associated with HLH.

Key words: hemophagocytic lymphohistiocytosis, lymphoma, autoimmune diseases, clinical manifestation, prognosis, risk factor

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Abbreviations: AOSD = adult-onset Still disease, CNS = central nervous system, DIC = disseminated intravascular coagulation, CMV = cytomegalovirus, EBV = Epstein-Barr virus, HLH = hemophagocytic lymphohistiocytosis, IVIg = intravenous immunoglobulin, MAS = macrophage-activation syndrome, NK = natural killer, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome caused by a highly active but ineffective immune response, including impaired or absent function of natural killer (NK) cells and cytotoxic T cells, and the release of proinflammatory cytokines.[6] Patients with HLH present with a wide spectrum of clinical manifestations and their conditions may rapidly deteriorate, resulting in considerable morbidity and mortality. The primary form, familial HLH, typically seen during infancy and early childhood, is inherited as a recessive trait, and has been well studied.[7,8] Adult-onset HLH is often secondary to an underlying disease, such as infection, malignancy, or autoimmune disease.[8] To improve the recognition and understanding of this potentially life-threatening disorder, we analyzed data from 103 patients hospitalized with HLH over a 15-year period. To our knowledge, this is the largest cohort of adult HLH patients in the literature.

PATIENTS AND METHODS

Patients

From patients' medical records we identified patients who were diagnosed with or considered to have HLH admitted to Peking Union Medical College Hospital from January 1997 to June 2012, excluding patients aged younger than 16 years old. The diagnosis of HLH was based on the HLH diagnostic criteria revised by the Histocyte Society in 2004 (HLH-2004).[7] Patients were required to fulfill 5 of the following 8 criteria: 1) fever; 2) splenomegaly; 3) cytopenia affecting at least 2 of 3 lineages in the peripheral blood, (hemoglobin <90 g/L, platelets $<100 \times 10^9$/L, neutrophils $<1.0 \times 10^9$/L); 4) hypertriglyceridemia (≥3 mmol/L) and/or hypofibrinogenemia (≤1.5 g/L); 5) hemophagocytosis in bone marrow, spleen, or lymph nodes; 6) low or absent NK cell activity; 7) hyperferritinemia (≥500 ug/L); and 8) increased soluble CD25 (that is, soluble interleukin-2 receptor, [sIL-2r]) levels ≥2400 U/mL. Because tests of soluble CD25 levels and NK cell activity were not available in our institution, we enrolled only the HLH patients who fulfilled 5 or more of the 6 other criteria. None of the patients underwent genetic testing. The local institutional review board approved the study. Because the study was based on a review of medical records that had been obtained for clinical purposes, the requirement for written informed consent was waived.

Methods

We retrospectively reviewed the patients' medical records and collected clinical data about underlying diseases, probable triggers for HLH onset, clinical manifestations, laboratory findings, treatments, and outcomes. Cytomegalovirus (CMV)

infection was defined by positive CMVpp65 antigenemia with at least 1 of the following clinical manifestations: fever, pneumonia, cytopenia, or liver function abnormality. Paired serum samples were also collected to detect CMV antibodies titers. A fourfold rise in IgG anti-CMV titers or a significantly elevated level of IgM antibody helped to confirm the diagnosis of active CMV infection.[19] Epstein-Barr virus (EBV) infection was diagnosed based on the detection of IgA or IgM antibodies against virus capsid antigen or high levels of EBV DNA.[17] Disseminated intravascular coagulation (DIC) was defined as prolonged prothrombin time, hypofibrinogenemia, or increased fibrinogen degradation products.[12]

Statistical Analysis

Numerical data and categorical data were expressed as the mean ± SD (range) and percentage respectively. As no data were distributed normally, we used the Mann-Whitney U test to compare quantitative variables. Categorical variables were compared by the Pearson chi-square test. We used multivariate logistic regression analysis to identify the independent risk factors for survival. All tests of significance were 2-sided, and a p value of < 0.05 was considered significant. All statistical analyses were processed using SPSS 13.0 for Windows.

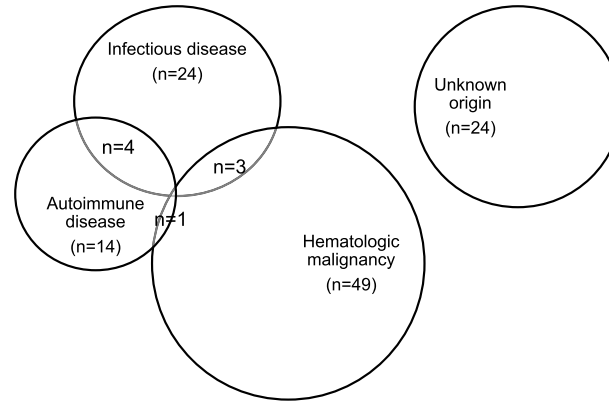

FIGURE 1. Proportion of underlying diseases in 103 adult patients with HLH (see Table 1). (Eight patients had a combination of underlying diseases.)

RESULTS

Demographic Features and Underlying Diseases

A total of 103 patients with HLH (54 male, 49 female) met the criteria for analysis. The diagnosis of HLH was made at

TABLE 1. Underlying Diseases of 103 Patients With HLH

Underlying Disease	No. of Patients	%
Hematologic malignancies*	49	47.6
Peripheral T-cell lymphoma	18	17.5
Unclassified lymphoma	12	11.7
T-cell lymphoma†	7	6.8
Subcutaneous panniculitis-like T-cell lymphoma	5	4.9
B-cell lymphoma	4	3.9
NK/T-cell lymphoma	2	1.9
Intravascular T-cell lymphoma	1	0.97
Infectious disease	24	23.3
Viral infection	16	15.5
Epstein-Barr virus	8	7.8
Cytomegalovirus	6	5.8
Coxsackie virus	1	0.97
Herpes simplex virus	1	0.97
Bacterial infection	8	7.8
Tuberculosis	4	3.9
Autoimmune diseases	14	13.6
Connective tissue disease	3	2.9
Adult-onset Still's disease‡	2	1.9
Rheumatoid arthritis‡	2	1.9
Systemic lupus erythematosus	2	1.9
Dermatomyositis	2	1.9
Granulomatosis with polyangiitis (Wegener's)§	1	0.97
Primary Sjögren syndrome	1	0.97
Crohn's disease§	1	0.97
Unknown origin	24	23.3

*Three patients had lymphoma complicated by EBV infection.

†One patient had T-cell lymphoma complicated by dermatomyositis.

‡Two patients had cytomegalovirus infection with underlying rheumatoid arthritis and adult-onset Still's disease, respectively.

§Two patients had sepsis complicated with granulomatosis with polyangiitis (Wegener's granulomatosis) and Crohn's disease, respectively.

mean age 39.2 ± 17.7 yr (range, 16–78 yr). The underlying diseases of HLH patients were mostly hematologic malignancies (n = 49, 47.6%), followed by infectious diseases (n = 24, 23.3%) and autoimmune disorders (n = 14, 13.6%) (Table 1). In 24 cases, no underlying disorder was identified (Figure 1). In HLH patients with infectious diseases, 16 patients (16/24, 66.7%) had a viral infection, and 4 patients had tuberculosis. Eight patients had a combination of findings. Three patients were diagnosed with lymphoma complicated by EBV infection, 1 patient had T-cell lymphoma complicated by dermatomyositis, 2 patients had CMV infection with underlying rheumatoid arthritis (RA) and adult-onset Still's disease (AOSD) respectively, and 2 patients had sepsis complicated by granulomatosis with polyangiitis (Wegener's granulomatosis) and Crohn's disease respectively. Nineteen patients were formerly diagnosed as having unclassified lymphoma by bone marrow biopsy. We reviewed those patients' records and tissue slides with a hematologist and a pathologist. Seven patients were further classified as having T-cell lymphoma. Because of the limitation of diagnostic technology and their rapid clinical deterioration, 12 patients did not achieve a more specific diagnosis during their hospitalization and can only be diagnosed as having unclassified lymphoma.

Clinical Features

The clinical manifestations varied significantly (Table 2). Nearly all HLH patients (96.1%) had intermittent high fever. Signs of reticuloendothelial system activation were prominent, including splenomegaly (79.6%), hepatomegaly (65.0%), and lymphadenopathy (53.4%). Among patients with lymphadenopathy, 39 had superficial lymphadenopathy, 36 had visceral lymphadenopathy, and 20 patients had both superficial and visceral lymphadenopathy. Other problems included proteinuria (31.1%), gastrointestinal hemorrhage (14.6%), DIC (13.6%), central nervous system (CNS) disorders (12.6%) including altered mental status (9.7%) and cranial hemorrhage (2.9%), and increased creatinine (7.8%).

Laboratory Findings

At the time of HLH diagnosis, cytopenia could be seen in almost all cases (101/103, 98.1%). Thrombocytopenia ($<100 \times 10^9$/L), leukopenia ($<4.0 \times 10^9$/L), and anemia (<90 g/L) occurred in 86.4%, 77.7%, and 59.2% of cases, respectively. Most patients had some degree of impaired liver function, with elevated aspartate aminotransferase (84.3%), alanine aminotransferase (83.5%), and hyperbilirubinemia (59.0%). Elevation of lactate dehydrase (98.9%) was remarkable not only in patients with lymphoma or liver dysfunction (Table 3).

Significantly increased serum ferritin level (>500 μg/L, 63/64, 98.4%), hypertriglyceridemia (54/61, 88.5%), and hypofibrinogenemia (≤1.5 g/L, 56/92, 60.9%) were widely documented, being consistent with the diagnostic criteria of HLH. Hemophagocytosis was found in bone marrow smears of 90 patients (90/103, 87.4%) and spleen biopsies of 2 patients. Although we could not test for NK cell activity in our institution, a reduction of NK cell number (38/43, 88.4%) was found in many patients.

Elevated C-reactive protein level and increased erythrocyte sedimentation rate were found in 93.7% (59/63) and 65.8% (48/73) of cases respectively.

TABLE 2. Clinical Manifestations of 103 Patients With HLH

Clinical Manifestation	No. of Patients	%
Fever	99	96.1
Splenomegaly	82	79.6
Hepatomegaly	67	65.0
Lymphadenopathy	55	53.4
Renal impairment	35	34.0
New-onset proteinuria	32	31.1
Increased creatinine	8	7.8
Gastrointestinal hemorrhage	15	14.6
Disseminated intravascular coagulation	14	13.6
Central nervous system involvement	13	12.6
Altered mental status	10	9.7
Intracranial hemorrhage	3	2.9

TABLE 3. Laboratory Findings of 103 Patients With HLH

Laboratory Finding	No. of Patients	%
Cytopenia	101/103	98.1
Thrombocytopenia ($<100\times10^9$/L)	89/103	86.4
Leukopenia ($<4.0\times10^9$/L)	80/103	77.7
Neutropenia (neutrophils $<1.0\times10^9$/L)	76/103	73.8
Anemia (hemoglobin <90 g/L)	61/103	59.2
Liver function impairment	101/103	98.1
Elevated alanine aminotransferase	81/97	83.5
Elevated aspartate aminotransferase	70/83	84.3
Elevated total bilirubin level	49/83	59.0
Elevated lactate dehydrase	88/89	98.9
Hypofibrinogenemia	56/92	60.9
Hypertriglyceridemia	54/61	88.5
Increased serum ferritin	63/64	98.4
Reduced natural killer cell number	38/43	88.4
Increased erythrocyte sedimentation rate	48/73	65.8
Elevated C-reactive protein level	59/63	93.7

Treatment and Outcomes

Among the 49 patients with malignancy-related HLH, 32 patients received systemic chemotherapy with CHOP or other doxorubicin-based regimens. Sixteen patients were also treated with etoposide, and 13 patients were treated with intravenous immunoglobulin (IVIg) (20 g/d for 3–5 consecutive days). Six cases with unclassified lymphoma, 3 cases with subcutaneous panniculitis-like T-cell lymphoma, and 1 case with diffuse large B-cell lymphoma had clinical remission and continued to receive periodic maintenance chemotherapy. The other 17 patients who did not receive chemotherapy because of poor performance status had no significant improvement after being treated with prednisone, cyclosporine A, etoposide, and IVIg. Overall, 39 patients (79.6%) died at the hospital or withdrew from further treatment (Figure 2).

Among the 11 cases with viral infection and without another clinical problem (such as cancer), 10 patients received more than 2 weeks of antiviral therapy. Ten patients were treated with prednisone at doses of 0.5–1.0 mg/kg per day, and 2 patients with methylprednisolone pulse therapy (1.0 g/d for 3 d), 5 patients with IVIg (20 g/d for 3–5 d), 5 patients with cyclosporine A, and 4 patients with etoposide. Compared with the high in-hospital mortality of patients with malignancy-related HLH, patients with viral infection-related HLH had much better outcomes, with 50% (8/16) of cases surviving after appropriate

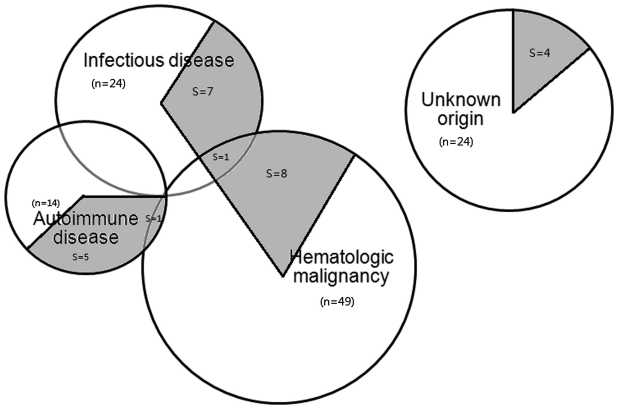

FIGURE 2. Patient outcome in different subgroups of underlying diseases. Among the 49 patients with malignancy-related HLH, only 10 patients (20.4%) survived including 1 patient with dermatomyositis and 1 with EBV infection. Among the 14 patients with autoimmune-related HLH, 6 patients survived (42.9%). Among the 24 patients with infection-related HLH, 8 of the 16 patients (50%) with viral infection-related disease survived, but none of the 8 patients with bacterial infection-related disease survived.

medical interventions, including 1 patient who had lymphoma complicated with EBV infection (see Figure 2). Four patients with tuberculosis infection died despite prompt antituberculosis and supportive treatment.

For the 14 cases with autoimmune-related HLH, systemic corticosteroids (equivalent to 0.5–1.0 mg/kg per day of prednisone) combined with immunosuppressive agents (cyclophosphamide, methotrexate, or cyclosporine A) were given to treat the underlying diseases. Four patients received methylprednisolone pulse therapy, 8 patients received IVIg, and 3 patients received etoposide. Patients with EBV or CMV infection also received antiviral therapy (10 of 11 patients who were suspected or confirmed as having EBV infection received intravenous ganciclovir infusion). Six patients (6/14, 42.9%) achieved clinical remission, including the patient who had lymphoma complicated with dermatomyositis (see Figure 2).

For those 24 patients with HLH of unknown origin, 18 patients were treated with prednisone at the initial dosage of 30–40 mg/day, 7 patients with etoposide, 23 patients with empirical antiviral therapy, and 8 patients with IVIg. However, only 4 patients achieved clinical improvement (4/24, 16.7%) (see Figure 2).

None of the patients in the current study received hematopoietic cell transplantation before treatment. Among 22 patients who received cyclosporine, 8 patients had proteinuria, 1 patient had a slightly increased serum creatinine level, and 2 patients had CNS involvement. None had exacerbation of renal or CNS disease after treatment with cyclosporine.

The overall mortality rate was 74.8% (77/103). Of the patients who died, 39 more likely died related to the malignancy than the HLH. Ten patients probably died of HLH-related organ hemorrhage and coagulopathy, including DIC, intracranial hemorrhage, gastrointestinal hemorrhage, and diffuse alveolar hemorrhage. The other 28 patients possibly died of HLH, but alternative causes such as sepsis and multiple organ dysfunction syndrome of undetermined origin could not be excluded definitely. The duration from the onset of HLH to death varied from 24 days to 16 months, with a median duration of 1.5 months. Of the 26 patients (25.2%) who survived, 19 (18.4%) were followed for 1–28 months (median duration, 8 mo) and remained in remission.

We analyzed the correlation between outcome and possible factors that might affect the prognosis of HLH using the chi-square test (Table 4). The univariate analyses suggested that patients with older age at disease onset, male sex, splenomegaly, or thrombocytopenia might have a worse outcome. With the multivariant logistic analysis, male sex was the only factor associated with worse outcome (odds ratio, 4.734; 95% confidence interval, 1.604–13.97; $p < 0.05$).

DISCUSSION

HLH has a variable clinical spectrum, but patients with HLH typically presented with high fever, hepatosplenomegaly, cytopenia, coagulation abnormalities, pathologic evidence of hemophagocytosis, and fatal multiple organ failure.[6] It is thought that the clinical features are due to hypercytokinemia, as it has been reported that proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-10, IL-12, and IL-18, are released in large amounts by highly activated lymphocytes and macrophages.[13] Although the diagnostic and therapeutic guidelines for hereditary HLH have been developed and widely accepted, the causes of secondary (also referred to as "reactive") HLH remain to be unraveled. The 103 adult patients in the current study were thought to have reactive HLH, secondary to a variety of underlying diseases. However, underlying primary etiologies were not excluded by mutation analyses. The spectrum of the underlying diseases is fairly broad, and is consistent with the results previously reported in the literature.[8,18] In the current study, 47.6% patients had hematologic malignancy, 13.6% patients had infectious diseases, and 12.6% patients had autoimmune disorders.

It has been documented that a variety of viral, bacterial, fungal, rickettsial, mycobacterial, mycoplasma, and parasitic infections may trigger HLH.[16] Zhang et al[20] reported that EBV-associated HLH was more common in Asian populations, including HLH associated with EBV-related malignancies (mainly non-Hodgkin lymphoma). In the current study, although lymphoma was the most frequently identified cause of HLH, EBV was identified in only 3 (3/49, 6.1%) of the lymphoma patients. Viral infection-related HLH accounts for one-tenth of the whole group, but it is well known that the proportion of EBV infection in HLH decreases significantly after the age of 2 years.[9] Four patients (4/11, 36.4%) with uncomplicated viral infection-associated HLH died, compared with a much higher fatality rate (39/49, 79.6%) in the hematologic malignancy-related subgroup. When the decision for therapy is made, clinicians must weigh the benefits of suppressing macrophage activity against the potential risk of infection. Less aggressive immunosuppressive treatment strategies, such as high-dose IVIg, might be more suitable for patients with severe infection or immunologic compromise. Occurrence of tuberculosis combined with HLH is very rare. Only about 30 cases have been reported in the literature, with poor prognosis. All 4 patients with tuberculosis infection in the current study died, even after receiving prompt and proper antituberculosis and support treatment.

A special form of HLH developed in association with autoimmune diseases, termed macrophage-activation syndrome, which was found to be the underlying cause in 2%–5% of reactive HLH cases. Macrophage-activation syndrome occurs most commonly in the setting of systemic juvenile idiopathic arthritis, systemic lupus erythematosus, and AOSD, but occurrence with other autoimmune diseases such as systemic vasculitis, Sjögren syndrome, and systemic sclerosis has been reported.[2,4] In our series, 2 of 13 (15.4%) autoimmune-related HLH patients had AOSD. Emmenegger et al[5] have shown that some AOSD

TABLE 4. Factors that May Affect Prognosis of HLH

Factor	Alive	Dead	P
Cases (n)	26	77	
Age at onset (yr)	32.6±13.5	41.4±18.4	0.027*
Male sex	6	48	0.001**
Clinical manifestations			
Fever	25	74	0.991
Splenomegaly	17	65	0.037*
Hepatomegaly	13	54	0.063
Lymphadenopathy	14	41	0.810
Mental status change	1	9	0.243
Gastrointestinal hemorrhage	1	14	0.073
DIC	1	13	0.090
Laboratory findings			
Anemia (hemoglobin <90 g/L)	17/26	44/76	0.501
Thrombocytopenia	20/26	70/76	0.038*
Elevated alanine aminotransferase	23/24	60/73	0.099
Elevated aspartate aminotransferase	19/19	51/60	0.073
Elevated total bilirubin level	8/15	41/68	0.620
Elevated lactate dehydrase	22/23	66/66	0.088
Hypertriglyceridemia	15/16	39/45	0.445
Increased serum ferritin	18/18	45/46	0.528
Hypofibrinogenemia	14/26	43/66	0.315
Increased creatinine	1/22	7/71	0.437
Treatment			
Corticosteroids	22/26	61/76	0.623
Methylprednisolone pulse therapy	1/26	9/74	0.224
Etoposide	10/25	25/74	0.574
IVIg	11/26	24/72	0.413

*$p < 0.05$; **$p < 0.005$.

patients present with symptoms identical to HLH, and it may be difficult to separate a disease flare from a hemophagocytic episode. In a patient with known or suspected AOSD, some authors suggested that a drop of the typically increased white blood cell count or a decreasing erythrocyte sedimentation rate (due to hypofibrinogenemia) should direct attention to HLH.[3] The presence of extremely high serum ferritin and triglyceride levels during an AOSD disease flare also suggests HLH.[1] An increased serum vitamin B12 level was found to be associated with AOSD complicated by HLH, with a specificity of 75% and a sensitivity of 100%.[11]

Nearly half the patients (47.6%) in the current series had HLH in association with a hematologic malignancy. All patients had lymphoma, and 79.6% patients died, suggesting a very poor prognosis for patients in this category. The HLH manifestations may be masked and/or modified by the malignant process or therapeutic measures, so the diagnosis of HLH is often delayed. Rapid control of the malignant process often is not easily achieved, and cytostatic treatments further increase the risk of infectious complications.

In previous studies, the overall mortality associated with reactive HLH was reported to be 22%–60%.[2,5,16] The factors that affect patient survival are not known with certainty. Kaito et al[10] described poor prognostic factors of adult HLH, including age over 30 years, presence of DIC, hyperferritinemia, increased β2-microglobulin, jaundice, and worsening of anemia and thrombocytopenia. Lin et al[14] reported that a rapid fall of ferritin levels was associated with decreased mortality among pediatric patients with HLH. Park et al[15] found that an initial serum fibrinogen >166 mg/dL was associated with better patient survival. In the current series, the overall mortality rate was 74.8% (77/103). Among the patients who died, 16.9% (13/77) patients developed multiple organ dysfunction and 13.0% (10/77) had coagulopathies, including DIC, intracranial hemorrhage, gastrointestinal hemorrhage, and diffuse alveolar hemorrhage. When the correlation between clinical manifestations and outcome of HLH was analyzed, our results suggested that patients with older age at onset, male sex, splenomegaly, or thrombocytopenia are prone to have poor outcomes, although male sex was the only factor after multivariant analyses. Perhaps the differences between our study and the literature reports are related to the sample's proportion of underlying diseases.

In conclusion, we analyzed a single center's experience with adult patients with secondary HLH. HLH has a broad spectrum of etiologies. The clinical features vary significantly, and most patients progress to death. A bone marrow aspiration or organ biopsy revealing hemophagocytosis is helpful to confirm the diagnosis. The underlying cause is an important predictor of outcome, as is male sex. Prompt treatment with corticosteroids, immunosuppressants, and IVIg may improve the prognosis.

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