Arch Rheumatol 2023;38(x):i-xiii
doi: 10.46497/ArchRheumatol.2023.9728

ORIGINAL ARTICLE

A clinical analysis of hemophagocytic syndrome secondary to autoimmune diseases

Yang Liu[1,2], Qian Li[3], Yazhen Su[1,2], Guozhu Che[1,2], Ying Liu[1,2], Pengyan Qiao[1,2], Sumiao Liu[1,2], Ke Xu[1,2]

[1]*Department of Rheumatology and Immunology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China*
[2]*Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*
[3]*Department of Rheumatology and Immunology, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, China*

ABSTRACT

Objectives: This study aimed to analyze the differences of etiologies and clinical features between patients with autoimmune-associated hemophagocytic syndrome (AAHS) and those with other underlying diseases of hemophagocytic syndrome (HPS).

Patients and methods: The retrospective study was performed with 130 HPS patients (70 males, 60 females; mean age: 50.4±18.1 years; range, 13 to 85 years) between January 1st, 2011, and April 1st, 2022. The patients fulfilled at least five of the eight criteria proposed by the Histiocytosis Society in 2004. The underlying diseases related to HPS were divided into four categories: autoimmune, infection, malignancy and idiopathic diseases. And the clinical manifestations, laboratory examinations, treatments, and prognosis were analyzed respectively.

Results: Nineteen (14.6%) patients had AAHS, 45 (34.6%) had infection-associated HPS, 57 (43.8%) had malignancy-associated HPS, and nine (6.9%) had idiopathic HPS. The most common symptoms of HPS were unremitting fever in 123 (94.6%) of 130 patients and splenomegaly in 92 (70.8%). All patients manifested a decline of at least two lineages of hematopoietic cells. The absolute values of T cells and B cells of AAHS were significantly higher than that of malignancy-associated HPS. The levels of soluble CD25 (interleukin-2 receptor) of AAHS were the lowest among all-cause HPS ($p<0.05$). The all-cause mortality rate of hospitalized patients with HPS was 46.2%. The patients with AAHS had a better prognosis compared to other etiologies (odds ratio [OR]=0.091, 95% confidence interval [CI]: 0.011-0.775, p=0.028). Epstein-Barr virus infection (OR=4.761, 95% CI: 1.619-14.004, p=0.005) and pulmonary involvement (OR=4.555 95% CI: 1.524-13.609, p=0.007) were independent predictors of poor outcome in HPS. Thrombocytopenia (OR=0.978, 95% CI: 0.968-0.999, p=0.040) had a boundary effect on prognosis.

Conclusion: Patients with HPS secondary to autoimmune disease have better outcomes compared to patients complicated with Epstein-Barr virus infection or pulmonary involvement.

Keywords: Autoimmune diseases, hemophagocytic syndrome, macrophage activation syndrome.

Hemophagocytic syndrome (HPS) is caused by an uncontrolled immune response, whether familial or acquired, and a rare but life-threatening disease, leading to the overproduction of cytokines and a hyperinflammatory state.[1] Primary HPS occurs in children with inherited dysfunction of the immune response, particularly natural killer (NK) cells and cytotoxic T cells.[2] The condition subsequently leads to cytokine elevation and mononuclear phagocyte activation.[1,2] Secondary HPS is mainly encountered in adults and occurs after strong immunologic activation that accompanies systemic infection, immunodeficiency, or underlying malignancy, and sometimes more than one potential cause exists.[3] Caused by

Received: May 04, 2022 ***Accepted:*** August 22, 2022 ***Published online:*** December 01, 2022

Correspondence: Ke Xu, PhD. Department of Rheumatology and Immunology, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, 030032, China.
e-mail: zhaoxuke@hotmail.com

Citation:
Liu Y, Li Q, Su Y, Che G, Liu Y, Qiao P, et al. A clinical analysis of hemophagocytic syndrome secondary to autoimmune diseases. Arch Rheumatol 2023;38(x):i-xiii.

different predisposing diseases and conditions that are often mixed with different triggers, the heterogeneous pathogenic scenario in adults always results in a high mortality rate.[3] Patients with rheumatic immune diseases are mostly immunocompromised hosts, and HPS can occur with either a disease flare or an active infection from a complication of immunosuppressive treatment, making it a challenge to recognize HPS at the early stage.[4,5] HPS with autoimmune diseases may present different clinical features from other underlying diseases. Many previous case reports or small studies with limited sample sizes have focused the features on a specific adult-onset Still's disease (AOSD)[4] or systemic lupus erythematosus (SLE)-associated HPS.[5] Different from these studies, our retrospective study focused on the clinical differences between autoimmune-associated HPS (AAHS) and HPS with other kinds of underlying diseases in China, providing valuable information in the management of AAHS.

PATIENTS AND METHODS

Patients

The medical records of 130 HPS patients (70 males, 60 females; mean age: 50.4±18.1 years; range, 13 to 85 years) hospitalized in the Shanxi Bethune Hospital between January 1st, 2011, to April 1st, 2022, were retrospectively reviewed. The patients fulfilled at least five of the eight criteria proposed by the Histiocytosis Society in 2004.[6]

Definition of variables

The date of HPS diagnosis was defined as confirmation of fulfillment of HPS criteria by the attending physician. For patients with recurrent HPS, only the data related to the first hospitalization was considered. Variables assessed as prognostic factors for survival were collected by retrospective review of individual medical charts and classified into four groups.

Epidemiological features

The age at the time of diagnosis, sex, duration of disease, length of hospitalization, and active immunosuppression (defined as the use of glucocorticoids, immunosuppressive drugs, or biological therapies) were collected. AAHS was defined as having a known autoimmune disease or being diagnosed with a specific rheumatological disorder during the current presentation. Infection-associated HPS (IAHS) was defined as HPS in the setting of a confirmed viral, bacterial, or fungal infection. Notably, no cases of COVID-19 were collected since the Shanxi Bethune Hospital is not a designated hospital. Patients suffering active cancer, namely people who were treated for in the past six months or were newly diagnosed during the current presentation, were categorized as malignancy-associated HPS (MAHS). The conditions associated with HPS were not considered mutually exclusive, and patients could have more than one underlying disorder.

HPS features

Clinical features and organ involvements directly related to HPS were defined according to standard definitions. Laboratory values were collected as the maximum or minimum abnormal value measured during the HPS diagnostic process. Hemophagocytosis was defined as histological evidence of activated macrophages engulfing erythrocytes, platelets (PLTs), or nucleated cells in bone marrow smears or biopsy of bone marrow, liver, spleen, or lymph node.

Trigger factors of HPS

As a key differentiating aspect from previous studies, we classified trigger factors of HPS as disease flare, infection, and the first two concurrent factors in triggering the hyperinflammatory response. Clinical/microbiological evidence of active bacterial, viral, parasitic, or fungal infection identified during the HPS diagnostic process was confirmed by standard diagnostic procedures used in the standard of care practice of internal medicine.

Therapeutic interventions and prognosis

The HPS-related therapeutic regimens were classified as steroid, etoposide, cyclosporine, intravenous immunoglobulins (IVIGs), stem cell transplant, ruxolitinib, tocilizumab, plasma exchange, and antibiotics. The prognosis of HPS was defined according to the hospital mortality or survival. During the period of hospitalization, the causes of mortality were collected, including multiorgan failure (MOF),

sepsis-related respiratory failure, heart failure, hepatic encephalopathy, and disseminated intravascular coagulation (DIC).

Statistical analyses

All statistical analyses were conducted by IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables are shown as mean ± standard deviation (SD), and nonnormally distributed variables are presented as median and interquartile range. Categorical variables are summarized as absolute number with percentages. Differences between continuous variables were evaluated using Student's t-test or the Mann-Whitney U test. Chi-square analyses for categorical variables were conducted to compare the differences among various underlying diseases of HPS. The odds ratios (ORs) for HPS were evaluated by univariate analysis. The potential factors ($p<0.01$) showing univariate correlation were entered into the multivariate logistic regression model. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characterization

The mean age at diagnosis was 50.4±18.1 years. The initial department that the patients chose was the department of lymphatic oncology with 52 (40.0%) cases, followed by the department of hematology with 41 (31.5%) cases, the department of rheumatology and immunology with 24 (18.5%) cases, and the infectious disease department with six (4.6%) cases. The main group of underlying diseases consisted of autoimmune diseases in 19 (14.6%) patients, infections in 45 (34.6%), malignancies in 57 (43.8%), and idiopathic in nine (6.9%); 44 (33.8%) patients had two or more underlying diseases, whereas nine (6.9%) had no identified underlying disease/condition (Table 1). Among 19 AAHS patients, the underlying rheumatic diseases were AOSD in eight (42.1%), antiphospholipid syndrome in two (10.5%), SLE in two (10.5%), rheumatoid arthritis in two (10.5%), dermatomyositis in two (10.5%), Sjögren's syndrome in two (10.5%), and mixed connective tissue disease in one (5.3%) patient. The immunosuppressive treatment was reported in all autoimmune diseases at HPS diagnosis. The underlying diseases of IAHS and MAHS are detailed in Table 1. The mean duration of underlying autoimmune diseases (26.0±52.9 months) was significantly longer than that of other underlying diseases at the diagnosis of the episode of HPS ($p<0.05$).

Hemophagocytic syndrome features

Clinical features

The most common symptoms of HPS were unremitting fever in 123 (94.6%) of 130 patients and splenomegaly in 92 (70.8%). More than half of the patients (55.4%) were complicated

Table 1. Underlying diseases (n=130)

Underlying diseases	n	%
Autoimmune	19	14.6
Adult-onset Still's disease	8	6.2
Antiphospholipid syndrome	2	1.5
Systemic lupus erythematosus	2	1.5
Dermatomyositis	2	1.5
Rheumatoid arthritis	2	1.5
Sjogren's syndrome	2	1.5
Mixed connective tissue disease	1	0.8
Infection	45	34.6
Viral	26	20.0
Epstein-Barr virus	24	18.5
Human immunodeficiency virus	1	0.8
Influenza A	1	0.8
Bacterial	13	10.0
Staphylococcus epidermidis	2	1.5
Staphylococcus aureus	4	3.1
Brucella	6	4.6
Streptococcus pharyngealis	1	0.8
Fungal	1	0.8
Candida	1	0.8
Parasite	5	3.8
Leishmania donovani	5	3.8
Malignancy	57	43.8
Leukemia	3	2.3
Hairy cell leukemia	1	0.8
Acute lymphoblastic leukemia	1	0.8
Chronic myelomonocytic leukemia	1	0.8
Hodgkin lymphoma	4	3.1
Nodular lymphocyte-predominant	1	0.8
Hodgkin lymphoma	2	1.5
Mixed cell Hodgkin lymphoma	1	0.8
Nodular sclerosis Hodgkin lymphoma	47	36.2
Non-Hodgkin lymphoma	15	11.5
Diffuse large B-cell lymphoma	7	5.4
Angioimmunoblastic T-cell lymphoma	15	11.5
Natural killer/T cell lymphoma	8	6.2
Peripheral T-cell lymphoma	1	0.8
Mantle cell lymphoma	1	0.8
Anaplastic large cell lymphoma	2	1.5
Macroglobulinemia	1	0.8
Langerhans cell histiocytosis		
Idiopathic	9	6.9

Table 2. The clinical and laboratory features, treatment, and prognosis of HPS

The underlying diseases	Autoimmune (n=19)	Infection (n=45)	Malignancy (n=57)	Idiopathic (n=9)	Total (n=130)
Demographics					
Age at diagnosis (year) mean±SD	45.63±17.74	47.09±18.43	54.81±16.99	49.44±20.99	50.42±18.12
Female, n (%)	16/19 (84.2)	18/45 (40.0)	21/57 (36.8)	5/9 (55.6)	60/130 (46.2)
Duration of disease (months)	26.00±52.93	5.61±19.63	13.70±25.58	1.53±2.22	11.85±29.30
Length of hospitalization (days)	30.11±21.31	27.40±31.19	34.82±23.84	20.11±14.45	30.55±25.55
Trigger factor of HPS, n (%)					
Disease flare	9/19 (47.4)	0	23/57 (40.4)	9/9 (100)	41/130 (31.5)
Infection	0	45/45 (100)	0	0	45/130 (34.6)
Both	10/19 (52.6)	0	34/57 (59.6)	0	35/130 (26.9)
EB virus infection, n (%)	1/19 (5.3)	25/45 (55.6)	31/57 (54.4)	0	57/130 (43.8)
HPS related markers, n (%)					
Fever	16/19 (84.2)	44/45 (97.8)	54/57 (94.7)	9/9 (100)	123/130 (94.6)
Rash	7/19 (36.8)	1/45 (2.2)	6/57 (10.5)	3/9 (33.3)	17/130 (13.1)
Serous effusion	1/19 (5.3)	9/45 (20.0)	10/57 (17.5)	0/9 (0)	20/130 (15.4)
Pulmonary involvement	11/19 (57.9)	24/45 (53.3)	34/57 (59.6)	3/9 (33.3)	72/130 (55.4)
Gastrointestinal symptoms	4/19 (21.1)	13/45 (28.9)	13/57 (22.8)	4/9 (44.4)	34/130 (26.2)
Neurological features	2/19 (10.5)	9/45 (20.0)	3/57 (5.3)	2/9 (22.2)	16/130 (12.3)
Splenomegaly	11/19 (57.9)	37/45 (82.2)	38/57 (66.7)	6/9 (66.7)	92/130 (70.8)
Hepatomegaly	2/19 (10.5)	15/45 (33.3)	18/57 (31.6)	3/9 (33.3)	38/130 (29.2)
Peripheral lymphadenectasis	17/19 (89.5)	23/45 (51.1)	43/57 (75.4)	5/9 (55.6)	88/130 (67.7)
Liver dysfunction	15/19 (78.9)	36/45 (80.0)	38/57 (66.7)	6/9 (66.7)	95/130 (73.1)
Renal dysfunction	2/19 (10.5)	3/42 (7.1)	4/54 (7.4)	2/9 (22.2)	11/124 (8.9)
Anaemia (<90 g/L)	10/19 (52.6)	26/45 (57.8)	44/57 (77.2)	3/9 (33.3)	83/130 (63.8)
Thrombocytopenia (<100×10^9/L)	17/19 (89.5)	40/45 (88.9)	56/57 (98.2)	8/9 (88.9)	121/130 (93.1)
Neutropenia (<1.0×10^9/L)	7/17 (41.2)	24/44 (54.5)	36/57 (63.2)	2/9 (22.2)	69/127 (54.3)
Hypertriglyceridemia (>3 mmol/L)	7/17 (41.2)	12/43 (27.9)	19/55 (34.5)	2/9 (22.2)	40/124 (32.3)
Hypofibrinogenemia (<1.5 g/L)	8/18 (44.4)	27/45 (60.0)	33/56 (58.9)	4/9 (44.4)	72/128 (56.3)
sCD25 elevation (>6400 pg/mL)	13/14 (92.9)	20/21 (95.2)	22/22 (100)	5/6 (83.3)	60/63 (95.2)
Low NK cell function	12/14 (85.7)	16/21 (76.2)	19/22 (86.4)	6/6 (100)	53/63 (84.1)
Hemophagocytosis	15/16 (93.8)	31/38 (81.6)	42/47 (89.4)	3/7 (42.9)	91/108 (84.3)
DIC	8/19 (42.1)	10/45 (22.2)	19/57 (33.3)	3/9 (33.3)	40/130 (30.8)
Treatment given at diagnosis, n (%)					
MP pulse	4/19 (21.1)	7/45 (15.6)	18/57 (31.6)	0/9 (0)	29/130 (22.3)
Steroid	18/19 (94.7)	36/45 (80.0)	55/57 (96.5)	9/9 (100)	118/130 (90.8)
Etoposide	4/19 (21.1)	13/45 (28.9)	40/57 (70.2)	2/9 (22.2)	59/130 (45.4)
Cyclosporine	7/19 (36.8)	8/45 (17.8)	5/57 (8.8)	1/9 (11.1)	21/130 (16.2)
IVIG	11/19 (57.9)	19/45 (42.2)	28/57 (49.1)	3/9 (33.3)	61/130 (46.9)
Stem cell transplant	0/19 (0)	3/45 (6.7)	1/57 (1.8)	0/9 (0)	4/130 (3.1)
Ruxolitinib	3/19 (15.8)	4/45 (8.9)	0/57 (0)	1/9 (11.1)	8/130 (6.2)
Tocilizumab	2/19 (10.5)	0/45 (0)	1/57 (1.8)	1/9 (11.1)	4/130 (3.1)
Plasma exchange	5/19 (26.3)	1/45 (2.2)	0/57 (0)	0/9 (0)	6/130 (4.6)
Antibiotics	15/19 (78.9)	45/45 (100)	53/57 (93.0)	8/9 (88.9)	121/130 (93.1)
Prognosis, n (%)					
Improved	17/19 (89.5)	30/45 (66.7)	18/57 (31.6)	5/9 (55.6)	70/130 (53.8)
Dead	2/19 (10.5)	15/45 (33.3)	39/57 (68.4)	4/9 (44.4)	60/130 (46.2)
Cause of death, n (%)					
MOF	1/2 (50.0)	4/15 (26.7)	16/39 (41.0)	1/4 (25.0)	22/60 (36.7)
Respiratory failure, septic shock	-	7/15 (46.7)	15/39 (38.5)	1/4 (25.0)	23/60 (38.3)
Heart failure	1/2 (50.0)	-	-	-	1/60 (1.7)
Hepatic encephalopathy	-	1/15 (6.6)	-	1/4 (25.0)	2/60 (3.3)
DIC, shock	-	3/15 (20.0)	8/39 (20.5)	1/4 (25.0)	12/60 (20.0)

HPS: Hemophagocytic syndrome; SD: Standard deviation; EB: Epstein-Barr; NK: Natural killer; sCD25: Soluble IL-2 receptor (/sIL-2R); DIC: Disseminated intravascular coagulation; MP: Methylprednisolone; IVIG: Intravenous immunoglobulin; MOF: Multiorgan failure.

with pulmonary involvement and manifested acute respiratory distress requiring mechanical ventilation. Some patients (12.3%) who were severely ill presented with central nervous system involvement, including seizures, meningitis, and cerebral hemorrhage. There were also some nonspecific clinical features, such as rash (13.1%) and joint pain (13.1%), which are mostly related to autoimmune disease. Other clinical manifestations are presented in Table 2. There was no significant difference in clinical manifestations between AAHS and other underlying diseases of HPS.

Laboratory findings

All patients had suppression of at least two lineages of hematopoietic cells. The most common hematological abnormality was thrombocytopenia in 121 (93.1%) of 130 patients (Table 2). Hyperferritinemia (>500 ug/L) was present in all patients. Abnormalities in liver function were found in 73.1% of patients, disclosing frequently high levels of serum transaminases and lactate dehydrogenase and occasionally increased bilirubin levels. Moderate hypoalbuminemia was common. Additionally, raised triglycerides were found in 40 (32.3%) of 124 patients. There was often an abnormal coagulation profile, with hypofibrinogenemia in 72 (56.3%) of 128 and sharp increased D-dimers in all 130 patients. DIC was observed in 30.8% of patients. Soluble interleukin (IL)-2 receptor (sIL-2R/sCD25) levels were raised in 60 (95.2%) of 63, and NK cell activity was absent or lower in 53 (84.1%) of 63. Hemophagocytosis was detected in 91 (84.3%) of 108 cases (there was no histopathological study in the rest of 22 cases due to sudden death).

At the initial stage of diagnosis of AAHS, most patients' leukocytes, hemoglobin (HGB) and PLTs are within the normal or even higher reference value range (data not shown), while there's an inflammatory cascade reaction appeared concomitantly, along with the rapid decrease of total white blood cell or PLT at the late stage of disease course. Due to the large proportion of AOSD, the leukocyte levels of AAHS were slightly higher than that of other underlying disease of HPS, but there was no statistical difference (Supplement Table 1). Patients with AAHS were more likely to have higher levels of HGB and PLT and lower levels of C-reactive protein than that with MAHS ($p<0.05$). Patients with AAHS were more likely to have abnormal liver function tests, and their alanine aminotransferase and gamma-glutamyl transferase levels were higher than that of IAHS and MAHS ($p<0.05$), as well as the median cholesterol and high-density lipoprotein levels ($p<0.05$). The absolute values of T cells and B cells of AAHS were higher than that of MAHS ($p<0.05$). The levels of sCD25 of AAHS were the lowest among all-cause HPS ($p<0.05$). No significant difference in erythrocyte sedimentation rate, ferritin, or NK cell activity was revealed among the different underlying diseases of HPS. Additionally, no significant difference existed in other laboratory examination results (Supplement Table 1).

Hemophagocytic syndrome triggers

Disease flare-and-infection-triggered HPS was identified in over half of the patients (52.6%) with AAHS. The IAHS triggers included viral infections in 26 (57.8%) patients, bacterial infections in 13 (28.9%), parasitic infections in five (11.1%) (including five cases of Leishmania donovani), and fungal infections in one (2.2%). Similar to patients with AAHS, the MAHS was triggered by the active disease flare in 23 (40.4%) and coupled with infections in 34 (59.6%) patients. In note, Epstein-Barr virus (EBV) and malignancy can co-trigger HPS in the context of EBV-associated lymphoma. The all-cause HPS, infectious triggers were identified in up to 61.5% of patients, including infections alone in 45 (34.6%) and active diseases flare accompanied by infections in 35 (26.9%) patients. EBV infection was the predominant viral trigger, which presented in 57 (43.8%) of 130 patients.

Treatment and prognosis

Overall, specific therapies for HPS included glucocorticoids in 118 (98.8%) patients, etoposide in 59 (45.5%), cyclosporine in 21 (16.2%), IVIGs in 61 (46.9%), stem cell transplant in four (3.1%), ruxolitinib in eight (6.2%), tocilizumab in four (3.1%), and plasma exchange in six (4.6%) patients. The list of drugs and the therapeutic regimens used are summarized in Table 1. The all-cause mortality rate of hospitalized patients with HPS was 46.2%. The most common cause of death was sepsis-related respiratory failure (38.3%), closely followed by MOF (38.3%) and DIC (20.0%).

Factor	Univariate analysis		Multivariate analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Age	1.023(1.003~1.044)	0.027		
Autoimmune diseases	0.108(0.024~0.488)	0.004	0.091(0.011~0.775)	0.028
EB infection	3.500(1.692~7.239)	0.001	4.761(1.619~14.004)	0.005
Pulmonary involvement	3.111(1.503~6.438)	0.002	4.555(1.524~13.609)	0.007
DIC	1.938(0.911~4.121)	0.086		
LY	0.448(0.224~1.063)	0.071		
HGB	0.967(0.948~0.986)	0.001		
PLT	0.968(0.953~0.983)	0.001	0.978(0.968~0.999)	0.040
ALB	0.921(0.858~0.989)	0.023		
BUN	1.195(1.007~1.325)	0.001		
PT	1.281(1.099~1.493)	0.002		
The absolute values of T cells	0.999(0.998~1.000)	0.052		
The absolute values of Th cells	0.998(0.996~0.999)	0.011		
IL-10	1.000(1.000~1.001)	0.050		
IL-6	1.002(0.999~1.006)	0.032		

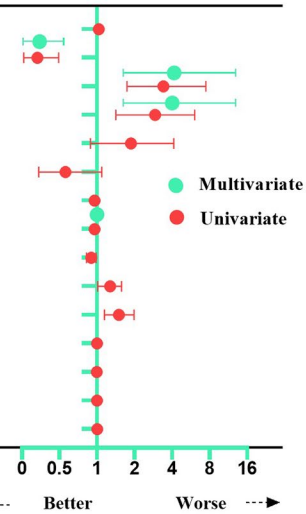

Figure 1. The univariate and multivariate logistic regression between the survival group and the death group for the prognosis of HPS.
OR: Odds ratio

CI: Confidence interval; EB: Epstein-Barr; DIC: Disseminated intravascular coagulation; LY: Leukocytes; HGB: hemoglobin; PLT: Platelet; ALB: Albumin; BUN: Blood urea nitrogen; PT: Prothrombin time; IL: Interleukin; HPS: Hemophagocytic syndrome.

The patients were divided into survival and death groups according to prognosis. The clinical and laboratory features, treatment of HPS between the survival and death group are summarized in supplement Table 2. Univariate logistic analysis demonstrated that the prognosis of adult HPS was affected by the following factors: sex, the underlying disease, EBV infection, pulmonary involvement, HGB, PLT, albumin, blood urea nitrogen (BUN), prothrombin time, the absolute values of T helper cells, and the level of IL-6 ($p<0.05$, Figure 1). Putting the above meaningful indicators into the logistic model, the forward stepwise method was used for multivariate analysis. Finally, the hospitalization survival analysis demonstrated that the patients with AAHS had a better prognosis compared with other etiologies (OR=0.091, 95% confidence interval [CI]: 0.011-0.775, p=0.028, Figure 1). EBV infection (OR=4.761, 95% CI: 1.619-14.004, p=0.005) and pulmonary involvement (OR=4.555, 95% CI: 1.524-13.609, p=0.007) were independent predictors of poor outcome in HPS. Thrombocytopenia (OR=0.978, 95% CI: 0.968-0.999, p=0.040) had a boundary effect on prognosis.

DISCUSSION

Hemophagocytic syndrome represents an uncontrolled inflammatory response, which is closely linked to high mortality.[3] The incidence of HPS was generally underestimated due to the similarity of clinical spectrum between the HPS and underlying disease exacerbation.[1,2] Among the patients with AAHS, females dominated the position with longer disease duration compared to that of other etiologies, which may be caused by the autoimmune disease characteristics.[4,5] AOSD is the main underlying disease of AAHS, and its incidence is higher than that of SLE, which is consistent with previous literature.[3] Although HPS was derived from different underlying diseases, it presented similarities in clinical and laboratory features. Noteworthily, pancytopenia, which was found at the late stage in AAHS, mainly due to the majority of AOSD, as these patients typically have elevated blood counts during disease flare.[1] In the early stage of HPS, secondary to AOSD, normal levels of these markers are inappropriate in the context of active inflammatory disease. The decline of blood cells is dynamic, and the absolute values

of laboratory results may be less helpful than that of the trend of results.[7]

Hemophagocytic syndrome may be the first clinical presentation of a rheumatologic or malignant disease triggered by the disease flare or by external triggers. In our study, 19 patients were diagnosed with rheumatic diseases before HPS treated with active immunosuppression. A variety of bacterial or viral infections were detected at the onset, which is consistent with previous reports,[8] confirming the complexity of the etiology of HPS secondary to autoimmune diseases. Immune disorder, hormone and immunosuppressant application, and granulocyte deficiency caused by HPS all make acquired immune deficiency syndrome patients prone to coinfection. The cytokine storm caused by HPS further aggravates the possibility of concurrent infection. A global retrospective analysis presented that viruses were the most common pathogens of HPS, among which EBV was the main pathogen in Asia,[9] followed by Brucella and Leishmania donovani, which is consistent with previous reports.[10] Elimination of triggers (mainly infections) is crucial for the treatment of adult patients with HPS.

Some studies proposed a new clinical entity of AAHS differing from infection-or malignancy-mediated HPS, and they speculated that the deposition of immune complexes or cytokine storm on hematopoietic cells might have triggered HPS.[11,14,15] The "cytokine storm," such as IL-1 and IL-6,[12,13] produced by uncontrolled tissue cells leads to the multisystem inflammatory response of the body and results in MOF.[14,15] In our research, lymphocyte subset function showed that the activity of NK cells significantly decreased, CD3 and CD4 cells decreased, CD8 increased, and IL-6 was dramatically elevated in some patients, which supported the view that HPS has abnormal immune function. The NK cell activity and sCD25 levels were not measured regularly in the majority of hospitals and may be of low interest for the diagnosis of the reactive form of the syndrome.

The treatment consists of therapies for the underlying disease, as well as cytokine storm or autoantibody production. Standard treatment for AAHS has not yet been established, but most cases are treated with immunosuppressive agents with a relatively good response. Although the place of cytokine blockers in the management of macrophage activation syndrome is still unclear, IL-6 inhibitors and JAK (Janus kinase) inhibitors represent a promising adjunctive therapy, particularly in refractory cases.[16,17] This prompted some groups, including ours, to treat severe AAHS with tocilizumab and ruxolitinib.[18] Therapeutic plasma exchange is used as a bridging therapy till other therapies have chances to work or till stem cell transplantation can be done,[19] which was also confirmed by Lorenz et al.'s[20] research on steroid refractory AAHS. Rituximab can be added to AAHS triggered by EBV as it can eliminate B cells where EBV proliferates. In general, whenever needed, supportive care, including prophylaxis for Pneumocystis jirovecii, fungal prophylaxis, and IVIG supplementation, should be similar to those for neutropenic patients.

In our study, the hospitalized all-cause mortality rate of HPS was 46.2%, in line with large series reported ranging between 42%[21] and 75%.[22] In line with our study, a better prognosis for AAHS was found with mortality rates of 13% in AAHS,[23] 9.5% in AOSD,[4] and 3% in SLE-associated HPS.[5] The patients with underlying neoplasia[21,24,25] had a poor prognosis compared to other etiologies. The wide list of prognostic factors identified until now for HPS may be due to the different frequencies of underlying diseases or source of heterogeneity. EBV infection, suggesting poor prognosis,[26] was the most common trigger of HPS. Therefore, studies on EBV genomes and clonality determination might prove useful. HPS can affect all organ systems, including the respiratory system. The most common cause of mortality was septic related respiratory failure (38.3%), which was more common in patients with HPS in intensive care units,[27] predicting poor prognosis. In our study, thrombocytopenia has a boundary effect on prognosis. However, a previous study found a PLT count $<39.5\times10^9$/L was an independent risk factor for 30-day survival in patients with HPS,[28] suggesting PLT changes dynamically when the patient's condition worsens or alleviates.[29] The changeable trend of PLT can be used as one of the indicators of survival and disease progression in HPS.

The results of our and other studies analyzing prognostic factors associated with survival in HPS should be evaluated with caution due to

the retrospective design and the lack of an international consensus on the management and treatment of adult HPS. Because of the rarity of the disease and the often-life-threatening presentation, prospective studies or randomized controlled trials in patients with HPS are extremely difficult, and it may be anticipated that the level of evidence will remain limited to retrospective studies. To overcome this issue, we chose to analyze the very early stage of mortality, which is more likely to capture the reasons of mortality due to the severity of the HPS rather than that related to underlying disease or treatment complications. However, in many cases, we acknowledge that it was impossible to precisely identify the cause of patient death, which is often combined.

In conclusion, our present study highlights the differences in the clinical characteristics and outcomes between patients with AAHS and those with other undying diseases of HPS. It adds rigorous evidence that patients with HPS secondary to autoimmune disease perform a better outcome, while the patients complicated with EBV infection or pulmonary involvement predict worse outcomes.

Ethics Committee Approval: The study protocol was approved by the Shanxi Bethune Hospital Ethics Committee (date 16.05.2022, no: YXLL-2022-056). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: The institutional review board waived the need for informed consent because of the retrospective design and the high rate of mortality.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study conception and design: Y.L.; Acquisition of data: Y.L., Q.L., Y.S.; Analysis and interpretation of data: Y.L.; Manuscript preparation: Y.L., Q.L., Y.S., G.C., Y.L., P.Q., S.L., K.X.; Statistical analysis: Y.L., Q.L., Y.S., G.C., Y.L., P.Q., S.L., K.X. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication, and took responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This work was supported by grants from the National Natural Science Foundation (81871292) and the Key Research and Development (R&D) Projects of Shanxi Province (201803D31136).

REFERENCES

1. Salunke B, Savarkar S, Patil VP. Hemophagocytic syndrome-an approach to the management. Indian J Crit Care Med 2019;23(Suppl 3):S191-S196.
2. Kerl K, Wolf IH, Cerroni L, Wolf P, French LE, Kerl H. Hemophagocytosis in cutaneous autoimmune disease. Am J Dermatopathol 2015;37:539-43.
3. Zhou M, Li L, Zhang Q, Ma S, Sun J, Zhu L, et al. Clinical features and outcomes in secondary adult hemophagocytic lymphohistiocytosis. QJM 2018;111:23-31.
4. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset Still disease: Clinical features, predictive factors, and prognosis in 21 patients. Medicine (Baltimore) 2015;94:e451.
5. Lambotte O, Khellaf M, Harmouche H, Bader-Meunier B, Manceron V, Goujard C, et al. Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. Medicine (Baltimore) 2006;85:169-82.
6. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
7. Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A multinational, multicenter study of 362 patients. Arthritis Rheumatol 2014;66:3160-9.
8. Brito-Zerón P, Bosch X, Pérez-de-Lis M, Pérez-Álvarez R, Fraile G, Gheitasi H, et al. Infection is the major trigger of hemophagocytic syndrome in adult patients treated with biological therapies. Semin Arthritis Rheum 2016;45:391-9.
9. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014;383:1503-16.
10. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465-77.
11. Takakuwa Y, Hanaoka H, Kiyokawa T, Iida H, Ishimori K, Uekusa T, et al. Adult-onset Still's disease-associated interstitial lung disease represents severe phenotype of the disease with higher rate of haemophagocytic syndrome and relapse. Clin Exp Rheumatol 2019;37 Suppl 121:23-7.

12. Ohata C, Koga H, Saruta H, Ishii N, Nakama T. Bacteremia in autoimmune bullous disease patients undergoing double-filtration plasmapheresis. J Dermatolog Treat 2019;30:402-4.
13. Brito-Zerón P, Kostov B, Moral-Moral P, Martínez-Zapico A, Díaz-Pedroche C, Fraile G, et al. Prognostic factors of death in 151 adults with hemophagocytic syndrome: Etiopathogenically driven analysis. Mayo Clin Proc Innov Qual Outcomes 2018;2:267-76.
14. Cancio M, Ciccocioppo R, Rocco PRM, Levine BL, Bronte V, Bollard CM, et al. Emerging trends in COVID-19 treatment: Learning from inflammatory conditions associated with cellular therapies. Cytotherapy 2020;22:474-81.
15. Yongzhi X. COVID-19-associated cytokine storm syndrome and diagnostic principles: An old and new Issue. Emerg Microbes Infect 2021;10:266-76.
16. Schulert GS, Minoia F, Bohnsack J, Cron RQ, Hashad S, KonÉ-Paut I, et al. Effect of biologic therapy on clinical and laboratory features of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2018;70:409-19.
17. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 2016;12:259-68.
18. Dufranc E, Del Bello A, Belliere J, Kamar N, Faguer S; TAIDI (Toulouse Acquired Immune Deficiency and Infection) study group. IL6-R blocking with tocilizumab in critically ill patients with hemophagocytic syndrome. Crit Care 2020;24:166.
19. Bosnak M, Erdogan S, Aktekin EH, Bay A. Therapeutic plasma exchange in primary hemophagocytic lymphohistiocytosis: Reports of two cases and a review of the literature. Transfus Apher Sci 2016;55:353-6.
20. Lorenz G, Schul L, Schraml F, Riedhammer KM, Einwächter H, Verbeek M, et al. Adult macrophage activation syndrome-haemophagocytic lymphohistiocytosis: 'of plasma exchange and immunosuppressive escalation strategies' - a single centre reflection. Lupus 2020;29:324-33.
21. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: A retrospective analysis of 162 patients. Am J Med 2014;127:1118-25.
22. Li F, Yang Y, Jin F, Dehoedt C, Rao J, Zhou Y, et al. Clinical characteristics and prognostic factors of adult hemophagocytic syndrome patients: A retrospective study of increasing awareness of a disease from a single-center in China. Orphanet J Rare Dis 2015;10:20.
23. Kumakura S, Murakawa Y. Clinical characteristics and treatment outcomes of autoimmune-associated hemophagocytic syndrome in adults. Arthritis Rheumatol 2014;66:2297-307.
24. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Am J Hematol 2015;90:220-4.
25. Schram AM, Comstock P, Campo M, Gorovets D, Mullally A, Bodio K, et al. Haemophagocytic lymphohistiocytosis in adults: A multicentre case series over 7 years. Br J Haematol 2016;172:412-9.
26. Huang L, Yao HX. Clinical therapy and prognostic analysis of 61 patients with secondary hemophagocytic syndrome. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2016;24:580-3.
27. Xu W, Qian R, Dai D, Xiao-Li L, Diao L, Zhao W. Clinical analysis of 32 adult patients with infection-associated hemophagocytic syndrome. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2020;32:797-802.
28. Zhao Y, Lu D, Ma S, Li L, Zhu J, Zhou D, et al. Risk factors of early death in adult patients with secondary hemophagocytic lymphohistiocytosis: A single-institution study of 171 Chinese patients. Hematology 2019;24:606-12.
29. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12:435-44.

Supplement Table 1. The laboratory features of HPS

Laboratory index (reference value range)	AAHS (n=19)	IAHS (n=45)	MAHS (n=57)	Idiopathic HS (n=9)	F/Z	*p*
WBC (×10⁹/L) (3.5-9.5)	2.76±2.40	2.07±1.94	1.84±2.60	2.46±1.13	0.847	0.471
N (×10⁹/L) (1.80-6.3)	1.91±1.87	1.31±1.33	1.16±1.66	1.60±1.04	1.105	0.350
LY (×10⁹/L) (1.10-3.20)	0.70±0.71	0.58±0.61	0.40±0.49	0.61±0.41	1.711	0.168
HGB (g/L) (115-150)	91.97±18.62	89.92±18.81	76.93±19.07*	94.33±23.89	5.848	**0.001**
PLT (×10⁹/L) (125-350)	67.76±52.03	46.20±41.60	29.81±25.56*	44.56±31.39	5.440	**0.001**
ESR (mm/h) (0-15)	34.20 (14.00, 63.50)	28.60 (8.00, 46.00)	47.33 (19.00, 68.00)	24.80 (14.00, 37.00)	5.272	0.153
CRP (mg/L) (0.00-8.00)	32.86 (2.50, 52.63)	65.64 (6.95, 95.46)	111.63 (31.52, 192,72)*	25.69 (15.86, 35.75)	12.545	0.006
RET (%) (0.5-1.5)	2.61±1.59	2.31±2.01	2.79±1.54	2.22±1.01	0.310	0.818
Ferritin (ng/mL) (23.9-336.2)	4946.64±6225.82	4067.73±4524.66	3376.00±10042.47	3574.81±4743.58	0.217	0.884
ALT (IU/L) (9-50)	513.24 (60.80, 1117.10)	197.74 (48.70, 214.20)*	85.78 (20.80, 143.45)*	428.36 (190.95, 705.90)	8.079	**0.044**
AST (IU/L) (15-40)	532.00 (42.60, 1012.88)	258.62 (54.80, 379.20)	91.73 (46.63, 122.68)	698.50 (199.05, 1388.45)	5.828	0.120
ALP (IU/L) (35-100)	250.86±229.01	192.81±146.99	264.70±271.87	232.36±238.35	0.737	0.532
GGT (IU/L) (7-45)	365.40 (131.05, 425.20)	149.29 (68.30, 178.80)*	47.60 (30.13, 71.30)*	244.24 (104.25, 368.90)	11.272	**0.010**
ALB (g/L) (40-55)	26.27±4.64	28.09±4.47	27.27±5.41	31.59±7.16	0.924	0.432
CK (IU/L) (40-200)	143.84±229.18	181.84±600.07	181.19±597.48	87.30±72.21	0.058	0.981
LDH (IU/L) (120-250)	1205.82±1287.08	1283.35±1309.58	1331.97±2039.78	925.43±489.93	0.137	0.938
HBDH (IU/L) (59-126.4)	787.76±768.78	787.65±637.89	956.32±1067.03	691.42±415.37	0.251	0.860
TG (mmol/L) (0.2-1.95)	2.81±1.21	2.40±1.18	2.64±1.29	3.14±2.06	1.010	0.391
CHO (mmol/L) (3.25-5.2)	4.45 (3.71, 5.11)	2.54 (1.60, 2.73)*	2.32 (1.64, 3.01)*	3.12 (2.28, 4.01)	21.23	**0.001**
LDL (mmol/L) (0-3.12)	2.59±0.89	1.64±0.70	1.78±0.73	1.98±0.65	5.108	**0.003**
HDL (mmol/L) (1.04-1.55)	0.97 (0.58, 1.39)	0.49 (0.23, 0.47)*	0.45 (0.18, 0.66)*	0.55 (0.39, 0.71)	19.403	**0.001**
Cr (umol/L) (74-110)	66.21±38.24	73.22±38.53	73.76±42.28	80.40±31.36	0.295	0.829
BUN (mmol/L) (3.1-8.0)	6.19±3.66	6.56±3.98	8.73±7.15	6.54±3.07	1.691	0.173
PT (s) (9.9-12.8)	12.60 (11.68, 13.65)	12.93 (12.30, 13.70)	16.30 (13.80, 18.53)	16.70 (12.60, 22.10)	2.042	0.564
APTT (s) (25.1-36.5)	34.47±7.90	37.34±6.79	34.70±6.99	35.33±12.76	1.213	0.308
FIB-C (g/L) (2.38-4.98)	2.06±1.66	1.70±1.05	1.87±1.25	1.59±0.70	0.514	0.673
D-Dimer (ng/mL) (0-243)	10249.40 (466.50, 9507.75)	4481.60 (842.00, 4959.00)	3546.50 (1938.00, 5789.00)	4859.00 (657.00, 9666.0)	3.198	0.362
The percentage of T cells (%) (65-79)	77.50±15.33	75.19±13.87	68.88±21.63	79.56±18.20	1.017	0.391

Supplement Table 1. Continues

Laboratory index (reference value range)	AAHS (n=19)	IAHS (n=45)	MAHS (n=57)	Idiopathic HS (n=9)	F/Z	*p*
The absolute counts of T cells (/μL) (650-1880)	754.9±642.55	536.61±389.52	297.77±252.70*	801.67±196.88	3.251	**0.031**
The percentage of Th cell (%) (34-52)	36.21±18.35	36.50±15.98	29.85±13.12	37.72±11.76	1.023	0.389
The absolute counts of Th cell (/μL) (340-1072)	338.55 (150.00, 431.00)	276.81 (89.25, 527.25)	116.82 (33.00, 234.00)	337.33 (323.00, 344.50)	12.274	**0.007**
The percentage of Ts cell (%) (21-39)	34.58±16.44	33.68±14.78	40.21±19.58	39.26±15.03	0.660	0.580
The absolute counts of Ts cell (/μL) (210-742)	355.09±376.44	268.75±218.48	165.00±151.81	427.33±202.00	1.875	0.148
Th/Ts (1-2)	2.21 (0.71, 1.39)	1.41 (0.56, 2.14)	0.85 (0.48, 1.07)	0.90 (0.50, 1.10)	3.436	0.329
The percentage of B cell (%) (9.02-14.1)	12.42±11.48	8.76±7.26	6.63±7.30	11.34±9.17	1.460	0.234
The absolute counts of B cell (/μL) (90-660)	97.91 (38.00, 183.00)	56.38 (22.25, 84.75)	24.06 (0.00, 25.00)*	194.67 (102.00, 241.00)	16.801	**0.001**
The percentage of NK cell (%) (4.6-16.0)	5.85±5.26	9.66±8.01	8.71±8.36	3.82±4.59	1.226	0.308
The absolute counts of NK cell (/μL) (46-590)	42.73 (13.00, 67.00)	72.94 (13.75, 115.25)	32.41 (3.50, 53.50)	70.67 (7.00, 102.50)	3.925	0.270
TNF (pg/mL) (0-8.4)	7.41 (4.30, 9.40)	13.16 (2.06, 15.75)	7.67 (2.99, 13.79)	11.35 (0.95, 16.55)	1.064	0.786
INFγ (pg/mL) (0-19.3)	14.68 (6.40, 26.22)	58.41 (14.30, 104.82)	54.72 (3.27, 103.25)	13.86 (1.38, 20.10)	3.302	0.347
IL-10 (pg/mL) (0-8.2)	266.56 (15.17, 80.60)	923.96 (5.75, 1769.28)	108.00 (15.24, 231.02)	43.67 (0.91, 65.05)	0.870	0.833
IL-6 (pg/mL) (0-18.9)	135.22 (17.10, 80.57)	82.96 (14.08, 108.88)	1148.29 (30.53, 2812.45)	90.04 (4.02, 133.05)	1.337	0.720
IL-4 (pg/mL) (0-11.2)	6.92 (1.19, 11.40)	6.32 (1.30, 11.45)	2.75 (0.18, 5.35)	10.13 (1.49, 14.45)	3.444	0.328
IL-2 (pg/mL) (0-10.7)	4.40 (2.07, 6.80)	4.50 (1.23, 8.67)	2.15 (1.33, 2.75)	7.55 (1.45, 10.60)	2.780	0.427
NK cell function (>15.11%)	11.52 (6.58, 15.30)	10.95 (2.17, 17.54)	12.66 (12.39, 15.84)	6.57 (2.21, 10.18)	4.654	0.199
sCD25 (<6400 pg/mL)	13989.60 (6221.33, 22448.50)	81288.4 (21701.25, 174633.25)*	348001.46 (15201.30, 182926.00)*	94159.14 (6332.35, 190358.00)*	12.310	**0.006**
IgA (g/L) (0.7-4.0)	3.05±1.62	2.45±1.83	1.92±1.38	2.31±1.75	1.536	0.212
IgG (g/L) (7-16)	13.29±5.66	13.48±7.08	10.85±5.98	7.72±2.95	2.371	0.077
IgM (g/L) (0.4-2.3)	1.30±0.75	1.24±0.97	2.22±6.32	0.95±0.72	0.465	0.708
C3 (g/L) (0.79-1.52)	1.14±0.39	0.90±0.31	0.83±0.36	1.16±0.37	2.123	0.113
C4 (g/L) (0.1-0.40)	0.25±0.13	0.28±0.11	0.27±0.16	0.24±0.04	0.222	0.881

PLT: Total platelet counts; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RET: Reticulocyte; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; ALB: Albumin; CK: Creatine kinase; LDH: Lactate dehydrogenase; HBDH: Hydroxybutyrate dehydrogenase; TG: Triglyceride; CHO: Cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; Cr: Creatinine; BUN: Urea nitrogen; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB-C: Fibrinogen; T cell: Total T cells (CD3 +); Th cell: T helper cell (CD3+CD4+); Ts cell: Suppressor T cells (CD3+CD8+); B cell: B cell (CD3-CD19+); NK cell: Natural killer cell (CD3-CD56+); TNF: Tumor necrosis factor; INFγ: Interferon γ; IL: Interleukin; sCD25: Soluble IL-2 receptor (/sIL-2R); *: Compared with AAHS; *: Indicates having statistical significance ($p<0.05$).

Supplement Table 2. The differences in clinical and laboratory features and treatments of HPS between the survival group and the death group

	The survival group (n=70)	The death group (n=60)	T/Z	*p*
Sex (male) n (%)	35/70 (50.0%)	35/60 (58.3%)	0.946	0.346
Age at diagnosis (year) mean±SD	47.12±17.28	54.27±18.45	-2.276	0.025
Course of disease (months)	10.36±30.94	13.60±27.43	-0.626	0.532
Length of stay (days)	28.49±24.25	32.95±27.95±27.00	-0.993	0.323
EB virus infection, n (%)	21/70 (30.0)	36/60 (60.0)	-3.576	**0.001**
Fever, n (%)	67 /70 (95.7)	56/60 (93.3)	0.596	0.552
Rash, n (%)	11/70 (15.7)	6/60 (10.0)	0.959	0.339
Serous effusion, n (%)	9/70 (12.9)	11/60 (18.3)	-0.900	0.370
Pulmonary involvement, n (%)	30/70 (42.9)	42/60 (70.0)	-3.201	**0.002**
Gastrointestinal symptoms, n (%)	16/70 (22.9)	18/60 (30.0)	-0.920	0.359
Neurological features, n (%)	11/70 (15.7)	5/60 (8.3)	1.275	0.205
Splenomegaly, n (%)	49/70 (70.0)	43/60 (71.7)	-0.207	0.837
Hepatomegaly, n (%)	19/70 (27.1)	19/60 (31.7)	-0.562	0.575
Peripheral lymphadenectasis, n (%)	51/70 (72.9)	37/60 (61.7)	1.359	0.176
Liver disfunction, n (%)	52/70 (74.3)	43/60 (71.7)	0.333	0.740
Renal disfunction, n (%)	6/70 (8.6)	5/60 (8.3)	0.147	0.884
Haemophagocytosis, n (%)	50/70 (71.4)	41/60 (68.3)	-0.740	0.461
DIC, n (%)	17/70 (24.3)	23/60 (38.3)	-1.737	0.085
WBC ($\times10^9$/L)	2.00±1.48	2.22±2.96	-0.531	0.596
N ($\times10^9$/L)	1.21±1.14	1.49±1.92	-1.011	0.314
LY ($\times10^9$/L)	0.60±0.49	0.42±0.63	1.858	0.065
HGB (g/L)	90.60±18.60	78.10±20.30	3.661	**0.001**
PLT ($\times10^9$/L)	55.87±42.58	25.93±25.10	4.777	**0.001**
ESR (mm/h)	26.29 (9.25, 41.50)	45.67 (23.50, 61.00)	-1.580	0.114
CRP (mg/L)	48.48 (6.30, 69.77)	78.98 (17.96, 175.97)	-1.610	0.107
RET (%)	2.54±1.91	2.50±1.50	0.075	0.940
Ferritin (ng/mL)	3727.79±4710.57	4022.34±10025.57	-0.219	0.827
ALT (IU/L)	385.03 (89.25, 481.63)	126.19 (23.43, 165.05)	-0.236	0.814
AST (IU/L)	480.64 (87.38, 518.13)	142.24 (51.13, 192.05)	-0.266	0.790
ALP (IU/L)	202.18±182.87	272.15±260.91	-1.612	0.110
GGT (IU/L)	251.88 (76.35, 306.92)	112.93 (36.03, 219.03)	-0.213	0.831
ALB (g/L)	29.00±5.06	27.12±5.17	2.065	**0.041**
CK (IU/L)	169.87±514.67	162.57±509.04	0.057	0.955
LDH (IU/L)	1156.94±1212.06	1412.54±2035.87	-0.843	0.401
HBDH (IU/L)	764.78±687.65	922.85±925.09	-0.803	0.425
TG (mmol/L)	2.47±1.15	2.79±1.47	-1.355	0.178
CHO (mmol/L)	3.31 (2.06, 4.17)	2.74 (1.84, 3.82)	-0.966	0.334
LDL (mmol/L)	1.95±0.82	1.79±0.78	0.845	0.401

Supplement Table 2. Continues

	The survival group (n=70)	The death group (n=60)	T/Z	*p*
HDL (mmol/L)	0.68 (0.33, 0.83)	0.53 (0.25, 0.71)	-2.129	**0.033**
Cr (umol/L)	71.44±37.33	74.51±41.87	-0.430	0.668
BUN (mmol/L)	5.83±3.22	9.27±7.01	-3.529	**0.001**
PT (s)	13.03 (11.78, 13.85)	15.73 (13.20, 16.30)	-3.520	**0.001**
APTT (s)	34.73±6.14	36.70±8.75	-1.481	0.141
FIB-C (g/L)	1.85±1.16	177±1.29	0.354	0.724
D-Dimer (ng/ml)	7171.75 (524.25, 5367.50)	3597.50 (766.25, 5177.25)	-1.138	0.255
The percentage of T cells (%)	77.68±13.10	68.07±21.62	2.210	0.031
The absolute counts of T cells (/μL)	611.46±494.09	376.00±323.20	1.833	**0.073**
The percentage of Th cell (%)	36.71±16.67	30.18±12.09	1.731	0.089
The absolute counts of Th cell (/μL)	282.07 (105.25, 385.75)	171.21 (41.00, 265.00)	-2.233	0.026
The percentage of Ts cell (%)	36.16±14.78	37.99±19.87	-0.420	0.676
The absolute counts of Ts cell (/μL)	312.36±292.92	186.69±153.82	1.713	0.094
Th/Ts	1.62 (0.56, 1.45)	0.98 (0.58, 1.09)	-0.378	0.706
The percentage of B cell (%)	8.84±7.96	8.59±8.92	0.121	0.904
The absolute counts of B cell (/μL)	70.00 (17.75, 91.75)	53.26 (2.00, 80.00)	-1.693	0.090
The percentage of NK cell (%)	8.20±7.54	8.17±7.89	0.011	0.991
The absolute counts of NK cell (/μL)	48.57 (13.75, 70.75)	54.74 (4.00, 73.00)	-0.759	0.448
TNF (pg/mL)	8.90 (2.3, 12.05)	13.03 (5.68, 18.53)	-2.187	0.029
INFγ (pg/mL)	40.64(4.37, 55.05)	32.41 (12.45, 63.99)	-0.726	0.468
IL-10 (pg/mL)	275.02 (5.90, 100.65)	875.56 (22.80, 1348.27)	-1.937	0.053
IL-6 (pg/mL)	94.88 (13.02, 100.65)	1001.49 (64.38, 2053.23)	-2.712	**0.007**
IL-4 (pg/mL)	5.70 (1.34, 10.30)	7.71 (0.22, 13.08)	-0.382	**0.703**
IL-2 (pg/mL)	3.92 (1.76, 5.60)	5.59 (1.52, 9.35)	-0.525	0.599
NK cell function (>15.11%)	11.50 (4.00, 16.02)	10.95 (6.56, 14.36)	-0.761	0.447
sCD25 (<6400 pg/ml)	214685.18 (7688.41, 68547.50)	89883.69 (18167.50, 182926.00)	-1.434	0.151
IgA (g/L)	2.39±1.44	2.47±2.02	-0.209	0.835
IgG (g/L)	12.79±6.34	11.00±6.25	1.216	0.228
IgM (g/L)	1.81±4.25	1.00±1.08	1.020	0.311
C3 (g/L)	1.03±0.38	0.98±0.36	0.484	0.631
C4 (g/L)	0.27±0.12	0.24±0.12	0.765	0.449
MP pulse, n (%)	11/70 (15.7)	18/60 (30.0)	-1.964	**0.052**
Steroid, n (%)	61/70 (87.1)	57/60 (95.0)	-1.545	0.125
Etoposide, n (%)	28/70 (40.0)	31/60 (51.7)	-1.331	0.186
Cyclosporine n (%)	13/70 (18.6)	8/60 (13.3)	0.805	0.422
IVIG, n (%)	29/70 (41.4)	32/60 (53.3)	-1.355	0.178

WBC: Total white blood cell; N: Absolute neutrophil count; LY: Absolute lymphocyte count; HGB: Hemoglobin; PLT: Total platelet counts; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RET: Reticulocyte; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; ALB: Albumin;CK: Creatine kinase; LDH: Lactate dehydrogenase; HBDH: Hydroxybutyrate dehydrogenase; TG: Triglyceride; CHO: Cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; Cr: Creatinine; BUN: Urea nitrogen; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB-C: Fibrinogen; T cell: Total T cells (CD3 +); Th cell: T helper cell (CD3+CD4+); Ts cell: Suppressor T cells (CD3+CD8+); B cell: B celL (CD3-CD19+); NK cell: Natural killer cell (CD3-CD56+); TNF: Tumor necrosis factor; INFγ: Interferon γ; IL: Interleukin; sCD25: Soluble IL-2 receptor (/sIL-2R); Ig: Immunoglobulin; C: Complement.