









## A clinical analysis of hemophagocytic syndrome secondary to autoimmune diseases

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### 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 1<sup>st</sup>, 2011, and April 1<sup>st</sup>, 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.<sup>1</sup> Primary HPS occurs in children with inherited dysfunction of the immune response, particularly natural killer (NK) cells and

cytotoxic T cells.<sup>2</sup> The condition subsequently leads to cytokine elevation and mononuclear phagocyte activation.<sup>1,2</sup> 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.<sup>3</sup> Caused by

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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.<sup>3</sup> 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.<sup>4,5</sup> 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)<sup>4</sup> or systemic lupus erythematosus (SLE)-associated HPS.<sup>5</sup> 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 1<sup>st</sup>, 2011, to April 1<sup>st</sup>, 2022, were retrospectively reviewed. The patients fulfilled at least five of the eight criteria proposed by the Histiocytosis Society in 2004.<sup>6</sup>

### 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  $\pm$  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  $50.4 \pm 18.1$  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 ( $26.0 \pm 52.9$  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

**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  |
| Sjögren'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 |
| <i>Staphylococcus epidermidis</i>  | 2  | 1.5  |
| <i>Staphylococcus aureus</i>       | 4  | 3.1  |
| <i>Brucella</i>                    | 6  | 4.6  |
| <i>Streptococcus pharyngealis</i>  | 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)  |
|--|-------------------|------------------|-------------------|------------------|----------------|
| <b>Demographics</b>                        |                   |                  |                   |                  |                |
| 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)  |
| <b>HPS related markers, n (%)</b>          |                   |                  |                   |                  |                |
| 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 <sup>9</sup> /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 <sup>9</sup> /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)  |
| Hyperfibrinogenemia (<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)  |
| <b>Treatment given at diagnosis, n (%)</b> |                   |                  |                   |                  |                |
| 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) |
| <b>Prognosis, n (%)</b>                    |                   |                  |                   |                  |                |
| 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)  |
| <b>Cause of death, n (%)</b>               |                   |                  |                   |                  |                |
| 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.

half of the patients (55.4%) were complicated 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

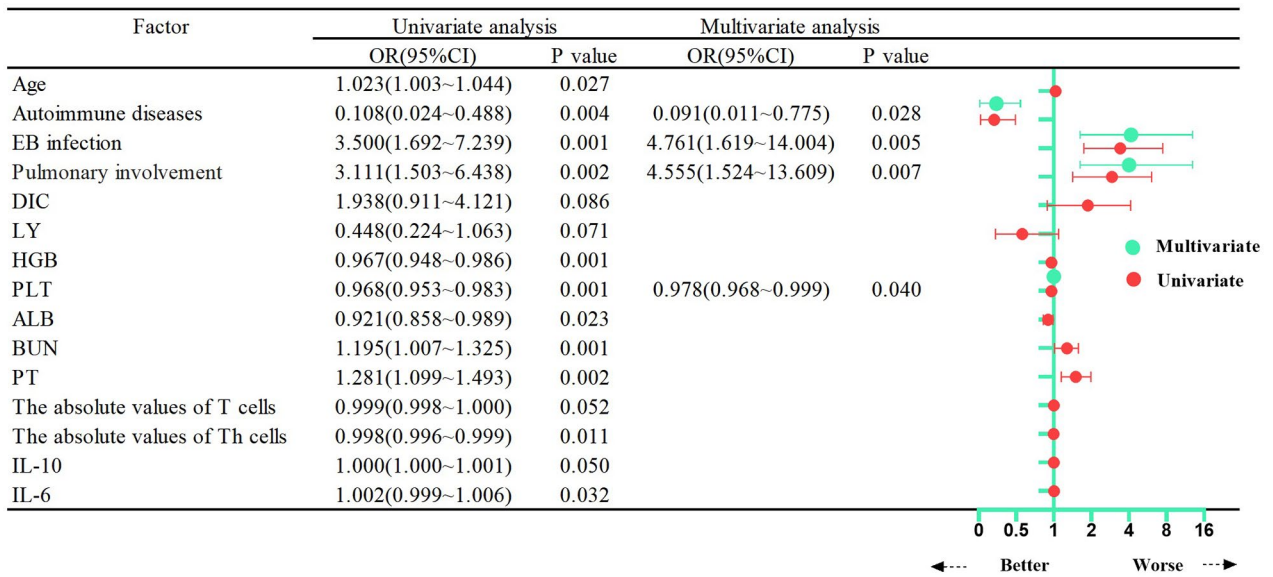
and lower levels of C-reactive protein than that with MAHS ( $p < 0.05$ ). Patients with AAHS were more likely to have abnormal liver function tests, and their alanine aminotransferase and gamma-glutamyl transferase levels were higher than that of IAHS and MAHS ( $p < 0.05$ ), as well as the median cholesterol 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



**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; Th cells: T helper cells; IL: Interleukin; HPS: Hemophagocytic syndrome.

(38.3%), closely followed by MOF (38.3%) and DIC (20.0%).

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.<sup>3</sup> The incidence of HPS was generally underestimated due to the similarity of clinical spectrum between the HPS and underlying disease exacerbation.<sup>1,2</sup> 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.<sup>4,5</sup> AOSD is the main underlying disease of AAHS, and its incidence is higher than that of SLE, which is consistent with previous literature.<sup>3</sup> 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.<sup>1</sup> 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.<sup>7</sup>

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,<sup>8</sup> 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,<sup>9</sup> followed by *Brucella* and *Leishmania donovani*, which is consistent with previous reports.<sup>10</sup> 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.<sup>11,14,15</sup> The "cytokine storm," such as IL-1 and IL-6,<sup>12,13</sup> produced by uncontrolled tissue cells leads to the multisystem inflammatory response of the body and results in MOF.<sup>14,15</sup> 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.<sup>16,17</sup> This prompted some groups, including ours, to treat severe AAHS with tocilizumab and ruxolitinib.<sup>18</sup> Therapeutic plasma exchange is used as a bridging therapy till other therapies have chances to work or till stem cell transplantation can be done,<sup>19</sup> which was also confirmed by Lorenz et al.'s<sup>20</sup> 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%<sup>21</sup> and 75%.<sup>22</sup> In line with our study, a better prognosis for AAHS was found with mortality rates of 13% in AAHS,<sup>23</sup> 9.5% in AOSD,<sup>4</sup> and 3% in SLE-associated HPS.<sup>5</sup> The patients with underlying neoplasia<sup>21,24,25</sup> 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,<sup>26</sup> 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,<sup>27</sup> predicting poor prognosis. In our study, thrombocytopenia has a boundary effect on prognosis. However, a previous study found a PLT count  $<39.5 \times 10^9/L$  was an independent risk factor for 30-day survival in patients with HPS,<sup>28</sup> suggesting PLT changes dynamically when the patient's condition worsens or alleviates.<sup>29</sup> 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.

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**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 ( $\times 10^9/L$ ) (3.5-9.5)        | 2.76 $\pm$ 2.40            | 2.07 $\pm$ 1.94           | 1.84 $\pm$ 2.60            | 2.46 $\pm$ 1.13          | 0.847  | 0.471        |
| N ( $\times 10^9/L$ ) (1.80-6.3)         | 1.91 $\pm$ 1.87            | 1.31 $\pm$ 1.33           | 1.16 $\pm$ 1.66            | 1.60 $\pm$ 1.04          | 1.105  | 0.350        |
| LY ( $\times 10^9/L$ ) (1.10-3.20)       | 0.70 $\pm$ 0.71            | 0.58 $\pm$ 0.61           | 0.40 $\pm$ 0.49            | 0.61 $\pm$ 0.41          | 1.711  | 0.168        |
| HGB (g/L) (115-150)                      | 91.97 $\pm$ 18.62          | 89.92 $\pm$ 18.81         | 76.93 $\pm$ 19.07*         | 94.33 $\pm$ 23.89        | 5.848  | <b>0.001</b> |
| PLT ( $\times 10^9/L$ ) (125-350)        | 67.76 $\pm$ 52.03          | 46.20 $\pm$ 41.60         | 29.81 $\pm$ 25.56*         | 44.56 $\pm$ 31.39        | 5.440  | <b>0.001</b> |
| 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 $\pm$ 1.59            | 2.31 $\pm$ 2.01           | 2.79 $\pm$ 1.54            | 2.22 $\pm$ 1.01          | 0.310  | 0.818        |
| Ferritin (ng/mL) (23.9-336.2)            | 4946.64 $\pm$ 6225.82      | 4067.73 $\pm$ 4524.66     | 3376.00 $\pm$ 10042.47     | 3574.81 $\pm$ 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  | <b>0.044</b> |
| 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 $\pm$ 229.01        | 192.81 $\pm$ 146.99       | 264.70 $\pm$ 271.87        | 232.36 $\pm$ 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 | <b>0.010</b> |
| ALB (g/L) (40-55)                        | 26.27 $\pm$ 4.64           | 28.09 $\pm$ 4.47          | 27.27 $\pm$ 5.41           | 31.59 $\pm$ 7.16         | 0.924  | 0.432        |
| CK (IU/L) (40-200)                       | 143.84 $\pm$ 229.18        | 181.84 $\pm$ 600.07       | 181.19 $\pm$ 597.48        | 87.30 $\pm$ 72.21        | 0.058  | 0.981        |
| LDH (IU/L) (120-250)                     | 1205.82 $\pm$ 1287.08      | 1283.35 $\pm$ 1309.58     | 1331.97 $\pm$ 2039.78      | 925.43 $\pm$ 489.93      | 0.137  | 0.938        |
| HBDH (IU/L) (59-126.4)                   | 787.76 $\pm$ 768.78        | 787.65 $\pm$ 637.89       | 956.32 $\pm$ 1067.03       | 691.42 $\pm$ 415.37      | 0.251  | 0.860        |
| TG (mmol/L) (0.2-1.95)                   | 2.81 $\pm$ 1.21            | 2.40 $\pm$ 1.18           | 2.64 $\pm$ 1.29            | 3.14 $\pm$ 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  | <b>0.001</b> |
| LDL (mmol/L) (0-3.12)                    | 2.59 $\pm$ 0.89            | 1.64 $\pm$ 0.70           | 1.78 $\pm$ 0.73            | 1.98 $\pm$ 0.65          | 5.108  | <b>0.003</b> |
| 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 | <b>0.001</b> |
| Cr (umol/L) (74-110)                     | 66.21 $\pm$ 38.24          | 73.22 $\pm$ 38.53         | 73.76 $\pm$ 42.28          | 80.40 $\pm$ 31.36        | 0.295  | 0.829        |
| BUN (mmol/L) (3.1-8.0)                   | 6.19 $\pm$ 3.66            | 6.56 $\pm$ 3.98           | 8.73 $\pm$ 7.15            | 6.54 $\pm$ 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 $\pm$ 7.90           | 37.34 $\pm$ 6.79          | 34.70 $\pm$ 6.99           | 35.33 $\pm$ 12.76        | 1.213  | 0.308        |
| FIB-C (g/L) (2.38-4.98)                  | 2.06 $\pm$ 1.66            | 1.70 $\pm$ 1.05           | 1.87 $\pm$ 1.25            | 1.59 $\pm$ 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 $\pm$ 15.33          | 75.19 $\pm$ 13.87         | 68.88 $\pm$ 21.63          | 79.56 $\pm$ 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  | <b>0.031</b> |
| 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 | <b>0.007</b> |
| 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 | <b>0.001</b> |
| 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 | <b>0.006</b> |
| 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 | <b>0.001</b> |
| 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 | <b>0.002</b> |
| 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 dysfunction, n (%)           | 52/70 (74.3)              | 43/60 (71.7)           | 0.333  | 0.740        |
| Renal dysfunction, 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 (×10 <sup>9</sup> /L)          | 2.00±1.48                 | 2.22±2.96              | -0.531 | 0.596        |
| N (×10 <sup>9</sup> /L)            | 1.21±1.14                 | 1.49±1.92              | -1.011 | 0.314        |
| LY (×10 <sup>9</sup> /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  | <b>0.001</b> |
| PLT (×10 <sup>9</sup> /L)          | 55.87±42.58               | 25.93±25.10            | 4.777  | <b>0.001</b> |
| 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  | <b>0.041</b> |
| 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 | <b>0.033</b> |
| 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 | <b>0.001</b> |
| PT (s)                               | 13.03 (11.78, 13.85)          | 15.73 (13.20, 16.30)           | -3.520 | <b>0.001</b> |
| 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  | <b>0.073</b> |
| 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 | <b>0.007</b> |
| IL-4 (pg/mL)                         | 5.70 (1.34, 10.30)            | 7.71 (0.22, 13.08)             | -0.382 | <b>0.703</b> |
| 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 | <b>0.052</b> |
| 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.