

Comparison of different treatment regimens and analysis of prognostic factors in secondary hemophagocytic lymphohistiocytosis in adults: A single-center retrospective study

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Abstract

Background. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease caused by immune hyperactivation. The overall survival (OS) of adults with secondary HLH remains suboptimal and new treatment strategies are needed.

Objectives. This study aimed to compare the efficacy of different regimens in the treatment of secondary HLH in adults and analyze the prognostic factors affecting patient survival.

Materials and methods. The clinical data of 245 adults with secondary HLH admitted to our hospital from January 2016 to October 2021 were analyzed retrospectively. The patients were divided into 3 groups according to different treatment regimens: corticosteroids therapy + chemotherapy + supportive treatment group (JHZ group), chemotherapy + supportive treatment group (HZ group) and corticosteroids therapy + supportive treatment group (JZ group). The clinical efficacy was compared among the 3 groups after treatment, and progression-free survival (PFS) and overall survival (OS) were calculated. Additionally, risk factors associated with prognosis were also analyzed with Cox regression analysis.

Results. The objective response rate (ORR) in the JHZ group was higher than that in the HZ group and JZ group, but there was no significant difference between the 3 groups. Also, the patients in the JHZ group had the longest OS and median PFS. Further Cox regression analysis suggested that hyperbilirubinemia was an independent risk factor for OS in secondary HLH patients.

Conclusions. A combination of corticosteroids therapy, chemotherapy and supportive therapy is superior to the other 2 regimens in the clinical benefit in the treatment of secondary HLH in adults, and thus may be a preferred and feasible treatment regimen. Moreover, hyperbilirubinemia was a risk factor for prognosis that has crucial guiding significance for clinical treatment of patients with secondary HLH.

Key words: supportive treatment, hyperbilirubinemia, chemotherapy, secondary hemophagocytic lymphohistiocytosis, corticosteroids therapy

Background

Hemophagocytic lymphohistiocytosis (HLH) can be triggered by primary (genetic factors) or secondary (non-genetic factors) causes. Primary HLH is usually inherited in an autosomal recessive pattern,¹ with a high incidence in young children, being relatively rare in clinical practice but showing high mortality. However, HLH is not a pediatric-specific disease and may occur at any age. According to current studies, the incidence of secondary HLH in adults accounts for about 40% cases of HLH.² The causes of secondary HLH include infections, autoimmune diseases and malignancies,³ but the pathogenesis of secondary HLH in adults has not been clarified. Adult patients with secondary HLH mainly present with symptoms of fever, organomegaly (lymphadenopathy, hepatomegaly or splenomegaly), neurological dysfunction, and liver dysfunction or coagulopathy (such as jaundice or bruising). Unfortunately, its clinical manifestations and laboratory parameters lack specificity, so it is difficult to diagnose it rapidly and treat it fully using immunosuppressive agents or chemotherapy in clinical practice. Moreover, the therapeutic effect of current treatment modalities on secondary HLH in adults is poor, and the prognosis is unsatisfactory.

There are no treatment regimens specifically developed for secondary HLH in adults, and most drugs used to treat HLH in adults are based on the HLH-94 or the HLH-2004 treatment protocols. Etoposide, dexamethasone and cyclosporin A are recommended in the HLH-94 protocol and have presented some efficacy.¹ HLH-2004 is a modification based on HLH-94, with basic treatment using etoposide, dexamethasone and cyclosporine A, and additionally with maximum supportive treatment (such as broad-spectrum antibiotics and gastric mucosal protective agents).⁴ Etoposide is a chemotherapeutic drug for malignant tumors, which ablates T cells involved in the pathophysiology of HLH.^{5,6} The mechanism of etoposide may induce normal apoptosis of interleukin (IL)-2-activated lymphocytes in HLH patients.⁷ In a retrospective study of children with HLH associated with EBV infection, the 2.5-year survival rate was significantly higher in children who received etoposide at 4 weeks compared to children who did not.⁸

Many case reports have confirmed that a combination of chemotherapy and corticosteroid therapy has a certain alleviating effect on secondary HLH in adults. Considering the toxic effect of chemotherapeutic drugs on patients may outweigh their benefits, some researchers tried to use corticosteroids combined with supportive therapy to treat adult HLH.⁹ Results showed clinical benefits and minimized toxic effect of chemotherapeutic drugs on patients.

Most existing studies on the treatment of secondary HLH in adults are case reports, and there is a lack of comprehensive and systematic analysis of the clinical efficacy of different treatment regimens in adult patients with secondary HLH.

Objectives

We aimed to preliminarily explore the preferred and feasible clinical treatment options for secondary HLH in adults by comparing different treatment options. Furthermore, we analyzed the related factors affecting the prognosis of patients using Cox regression analysis.

Materials and methods

Participants

This is a single-center retrospective study. Two hundred and forty-five adult patients with secondary HLH admitted to The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital from January 2016 to October 2021 were selected as the study participants. They were divided into 3 groups according to different treatment regimens: corticosteroids therapy + chemotherapy + supportive therapy group (JHZ group) (n = 56), chemotherapy + supportive therapy group (HZ group) (n = 108) and corticosteroids therapy + supportive therapy group (JZ group) (n = 81). Informed consent was given by all patients. This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital (approval No. 2019-SR-446).

Inclusion and exclusion criteria

All patients satisfying the HLH-2004 diagnostic criteria¹⁰ were selected: 1) age >18 years, with molecular diagnosis of HLH or diagnosis of X-linked lymphoproliferative syndrome; or 2) the presence of at least 3 of the following 4 criteria: fever lasting more than 7 days, body temperature >38.5°C; splenomegaly; cytopenias affecting ≥ 2 lineages (hemoglobin <90 g/L, platelets <100 × 10⁹/L, absolute neutrophil count <1.0 × 10⁹/L); hepatitis; and the presence of at least 1 of the following 4 criteria: hemophagocytosis in bone marrow, spleen or lymph node; elevated serum ferritin (≥ 500 µg/L); elevated soluble IL-2 receptor (sCD25) ($\geq 2,400$ U/mL); low or absent NK cell activity; and 3) other supporting evidence: hypertriglyceridemia (triglyceride level ≥ 3 mmol/L); hypofibrinogenemia (fibrinogen <1.5 g/L); hyponatremia.

Exclusion criteria were as follows: 1) patients with incomplete medical records and imaging data; 2) early patients; 3) patients treated with immune checkpoint inhibitors, but with no specific name and dose provided; 4) patients with 2 or more malignant tumors.

Treatment methods

In chemotherapy, etoposide injection (VP-16) (KPC Pharmaceuticals, Inc., Yunnan, China; 2 mL: 40 mg, batch No. H53021752) was infused intravenously (iv).

The injection was diluted with sodium chloride injection to reach a concentration not exceeding 0.25 mg/mL. The iv. infusion was performed for no less than 30 min per time. The dose and frequency of infusion was as follows: at weeks 1 and 2: 150 mg/m² – twice a week; at weeks 3 to 8: 150 mg/m² – once a week.

In corticosteroids therapy, dexamethasone tablets (Guangdong South Land Pharmaceutical Co., Ltd., Zhanjiang, China), 0.75 mg, batch No. H44024618) were selected with the dose of 10 mg/(m²·d) (daily dose of drug per square meter of body surface area) in weeks 1 and 2, 5 mg/(m²·d) in weeks 3 and 4, 2.5 mg/(m²·d) in weeks 5 and 6, and 1.25 mg/(m²·d) in week 7. Finally, the drug was discontinued in week 8.

Supportive therapy included active prevention and treatment of infection, blood transfusion therapy, enhancing immunity, and nutritional support.

Efficacy outcome measures

Objective response rate (ORR) refers to the proportion of patients whose tumor lesion volume shrink to the expected range and can maintain the minimum time required, which is the sum of complete response (CR) rate and partial response (PR) rate. Specifically, target lesion status was assessed according to RECIST 1.1 criteria¹¹: complete response (CR) – disappearance of all target lesions; partial response (PR) – at least a 30% decrease in the sum diameter of target lesions; progressive disease (PD) – at least a 20% increase in the sum diameter of target lesions; stable disease (SD) – response between PR and PD.

Overall survival (OS) is the time from the start of treatment to death, while progression-free survival (PFS) is the time from the start of treatment to the 1st recurrence/metastasis of the tumor or death of the patient. These 2 measures were mainly used to assess the clinical benefit of patients.

Statistical analyses

Experimental data were analyzed using IBM SPSS 22.0 (IMB Corp., Armonk, USA) software. The Shapiro–Wilk test was used to determine whether the continuous data conformed to normal distribution. The continuous data with non-normal distribution was expressed as median (interquartile range (IQR)) and analyzed using Kruskal–Wallis test. The categorical variables were expressed as incidence and percentage, and the difference between the 2 groups was assessed using the χ^2 or Fisher's exact tests. Progression-free survival and OS were described using the Kaplan–Meier method with the log-rank method for testing, and Bonferroni correction was used to control I-type error. Cox regression analysis was used to analyze independent risk factors for prognosis. For the Cox regression assumptions: 1) the martingale residuals test was used to test the proportional hazards assumption¹²;

2) the linearity assumption was utilized to determine whether the logarithm of the survival function was linear with respect to the continuous variable; 3) variance inflation factor (VIF) and tolerance (that is, the proportion of residuals obtained when regression analysis is performed on the other independent variables with each independent variable as the dependent variable) was used to test for multicollinearity between variables. A p-value <0.05 was considered statistically significant.

Results

Basic characteristics of patients

Two hundred and forty-five adult patients with secondary HLH were divided into 3 groups according to different treatment regimens: corticosteroids therapy + chemotherapy + supportive therapy group (JHZ group) (n = 56), chemotherapy + supportive therapy group (HZ group) (n = 108) and corticosteroids therapy + supportive therapy group (JZ group) (n = 81). Combining the results showed in Supplementary Fig. 1 and Supplementary Table 1, it was determined that the age values of the groups did not follow a normal distribution. Therefore, the Kruskal–Wallis test was used for analysis. There were no statistically significant differences between the 3 groups in general data such as age (p = 0.296), sex (p = 0.370), pathological type (infection-related, tumor-related, immune disease-related; p = 0.115), and smoking history (p = 0.913) (Table 1).

Therapeutic efficacy in the 3 groups

In the JHZ group, 23 patients had CR, 16 patients PR, 12 patients SD, and 5 patients PD, with an ORR of 69.64%. In the HZ group, including 43 patients had CR, 19 patients PR, 39 patients SD and 7 patients PD, with ORR of 57.41%. Finally, in the JZ group, there were 26 patients with CR, 17 patients with PR, 37 patients with SD, and 1 patient with PD, with ORR of 53.09%. The ORR (%) in the JHZ group was higher than that in the other 2 groups, but there was no significant difference in the efficacy among the 3 treatment regimens (p = 0.0143) (Table 2).

Prognostic analysis of patients in the 3 groups

Patients were followed up after treatment. The JHZ group was superior to the other 2 groups in terms of OS (p = 0.003). Also, the median PFS of the JHZ group (49 months) was significantly longer than that of the HZ group (29 months) and JZ group (26 months) (p < 0.001), suggesting that patients had the longest interval from the start of receiving treatment to the development of disease progression or patient death in the JHZ group (Fig. 1A,B).

Table 1. Basic characteristics of 245 adults with secondary hemophagocytic lymphohistiocytosis

Variable		JHZ group (n = 56)	HZ group (n = 108)	JZ group (n = 81)	H/F/ χ^2	p-value
Age [years]		53.5 (34.5, 63.50)	57.5 (44.0, 65.0)	57.0 (45.0, 66.0)	2.432	0.296 ^a
Sex (male/female)		34/22	74/34	48/33	1.990	0.370 ^b
Pathological type	infection-related	25	63	39	7.418	0.115 ^b
	tumor-related	17	31	20		
	immune disease-related	14	14	22		
Smoking history (no/yes)		19/37	36/72	25/56	0.182	0.913 ^b
ECOG score	<2	34	55	39	2.230	0.328 ^b
	≥ 2	22	53	42		
Malignant pleural effusion (no/yes)		39/17	79/29	60/21	0.351	0.839 ^b
PD-L1 expression (positive/negative)		17/39	22/86	18/63	2.134	0.344 ^b
EGFR gene mutation (positive/negative)		9/47	36/72	26/55	5.911	0.052 ^b
Brain metastasis (no/yes)		11/45	38/70	22/59	4.523	0.104 ^b
Surgical treatment (no/yes)		22/34	45/63	29/52	0.668	0.716 ^b
Immune-related adverse events (no/yes)		37/19	76/32	67/14	5.658	0.059 ^b
History of hormone therapy (no/yes)		42/14	80/28	50/31	4.171	0.124 ^b
Antibiotic history (no/yes)		41/15	81/27	51/30	3.469	0.177 ^b
Serum albumin	low	29	41	33	2.976	0.226 ^b
	high	27	67	48		
Serum calcium	low	28	41	33	2.239	0.327 ^b
	high	28	67	48		
Platelet content	<30 $\times 10^9$ /L	25	63	45	2.864	0.239 ^b
	$\geq 30 \times 10^9$ /L	31	45	36		
Fibrinogen	<1.0 g/L	27	67	47	2.895	0.235 ^b
	≥ 1.0 g/L	29	41	34		
Hyperbilirubinemia	≤ 17.1 μ mol/L	35	56	43	1.814	0.404 ^b
	>17.1 μ mol/L	21	52	38		

Data are expressed as median (interquartile range) or number. ^a Kruskal–Wallis test; ^b χ^2 test; JHZ group – hormone therapy + chemotherapy + supportive therapy; HZ group – chemotherapy + supportive therapy; JZ group – hormone therapy + supportive therapy.

Table 2. Comparison of efficacy among the 3 groups

Variable	JHZ group (n = 56)	HZ group (n = 108)	JZ group (n = 81)	χ^2	p-value
CR	23 (41.07%)	43 (39.81%)	26 (32.10%)	1.559	0.459
PR	16 (28.57%)	19 (17.59%)	17 (20.99%)	2.663	0.264
SD	12 (21.43%)	39 (36.11%)	37 (45.68%)	8.463	0.015
PD	5 (8.93%)	7 (6.48%)	1 (1.23%)	5.323	0.070 [#]
ORR (%)	39 (69.64%)	62 (57.41%)	43 (53.09%)	3.895	0.143

The data are n (%) and analyzed with χ^2 or Fisher's exact tests; [#] p-value was analyzed with Fischer's exact test; JHZ group – hormone therapy + chemotherapy + supportive therapy; HZ group – chemotherapy + supportive therapy; JZ group – hormone therapy + supportive therapy; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – objective response rate.

Prognostic factors affecting overall survival

First, the results of univariate Cox regression analysis showed that 8 potential variables (age, pathological type, Eastern Cooperative Oncology Group (ECOG) score, serum albumin, serum calcium, platelets content, fibrinogen, and hyperbilirubinemia) were associated with poor prognosis in adults with secondary HLH. For the Cox regression

assumptions, ECOG score and serum calcium did not satisfy the proportional hazards assumption (Supplementary Table 2). No significant violation of the linearity assumption was found for the continuous variable (age) (Supplementary Fig. 2). In addition, Supplementary Table 3 showed that there was no multicollinearity problem between the predictors. Therefore, variable screening was performed using the best subset algorithm with Bayesian information criterion (BIC)

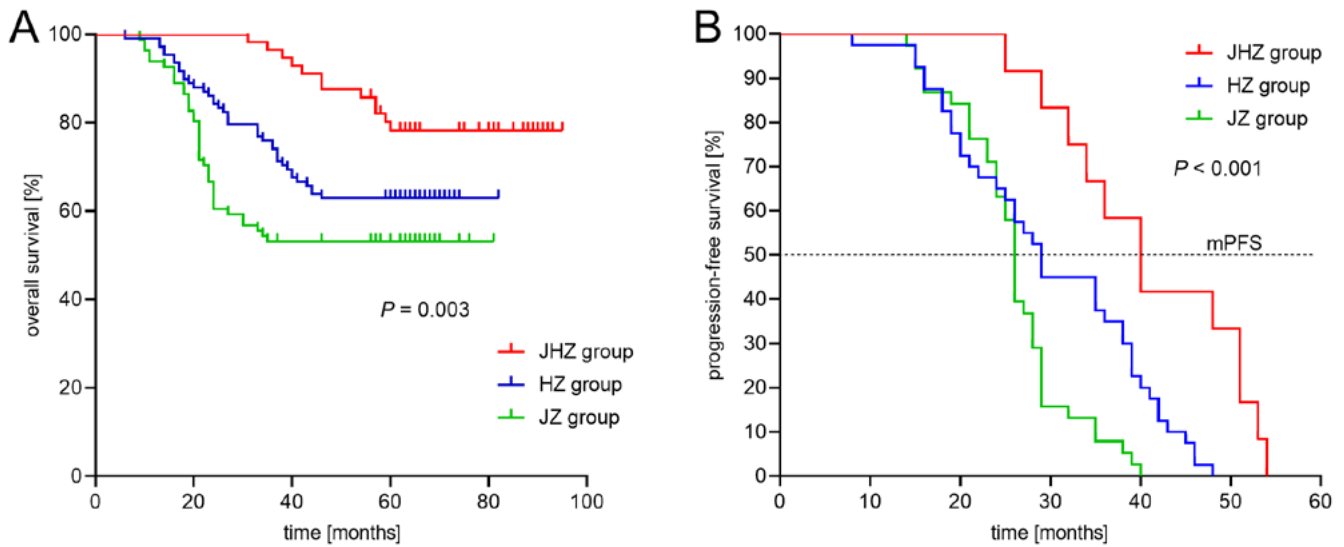


Fig. 1. Kaplan–Meier analysis of prognosis adults with secondary hemophagocytic lymphohistiocytosis (HLH) after treatment. A. Overall survival (OS); 12 (21.43%) in JHZ (hormone therapy + chemotherapy + supportive therapy) group (n = 56) were dead; 40 (37.04%) in HZ (chemotherapy + supportive therapy) group (n = 108) were dead; 38 (46.91%) in JZ (hormone therapy + supportive therapy) group (n = 81) were dead; B. Progression-free survival (PFS)

Table 3. Univariate and multivariate Cox regression analysis of factors affecting overall survival (OS)

Variable		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age		1.166 (1.139–1.193)	<0.001	1.220 (1.170–1.260)	<0.001
Sex		0.851 (0.549–1.319)	0.471	–	–
Pathological type	infection-related	1.000	–	1.000	–
	tumor-related	13.705 (7.903–23.769)	<0.001	3.170 (1.700–5.890)	<0.001
	immune disease-related	2.472 (1.218–5.017)	0.012	5.090 (2.120–12.200)	<0.001
Smoking history		0.963 (0.621–1.493)	0.866	–	–
ECOG score		3.401 (2.173–5.323)	<0.001	–	–
Malignant pleural effusion		0.870 (0.538–1.407)	0.570	1.000 (0.610–1.650)	0.992
PD-L1 expression		0.825 (0.261–2.608)	0.743	–	–
EGFR gene mutation		0.750 (0.484–1.163)	0.198	–	–
Brain metastasis		0.746 (0.481–1.156)	0.190	–	–
Surgical treatment		0.989 (0.649–1.508)	0.959	–	–
Immune-related adverse events		0.989 (0.620–1.578)	0.963	1.380 (0.830–2.300)	0.212
History of hormone therapy		0.807 (0.503–1.297)	0.376	–	–
History of antibiotic history		0.848 (0.531–1.353)	0.488	–	–
Serum albumin		2.719 (1.692–4.369)	<0.001	1.040 (0.520–2.110)	0.906
Serum calcium		0.398 (0.25–0.636)	<0.001	–	–
Platelet content		0.430 (0.275–0.672)	<0.001	–	–
Fibrinogen		0.445 (0.282–0.703)	0.001	0.950 (0.480–1.850)	0.869
Hyperbilirubinemia		9.532 (5.458–16.647)	<0.001	2.590 (1.280–5.260)	0.008

ECOG – Eastern Cooperative Oncology Group; 95% CI – 95% confidence interval; HR – hazard ratio.

as the criterion, and the variables entered into the multivariate analysis were age, pathological type, malignant pleural effusion, immune-related adverse events, serum albumin, fibrinogen, and hyperbilirubinemia. The multivariate analysis showed that age (hazard ratio (HR) = 1.220, 95% confidence interval (95% CI): 1.170–1.260; $p < 0.001$),

pathological type (tumor-related: HR = 3.170, 95% CI: 1.700–5.890; $p < 0.001$; immune disease-related adverse events: HR = 5.090, 95% CI: 1.120–12.200; $p < 0.001$) and hyperbilirubinemia (HR = 2.590, 95% CI: 1.280–5.260; $p = 0.008$) were independent risk factors for OS in adults with secondary HLH (Table 3).

Discussion

Hemophagocytic lymphohistiocytosis is characterized by excessive activation of macrophages and lymphocytes, which leads to excessive secretion of proinflammatory cytokines, resulting in tissue infiltration, organ failure and inflammation.¹³ Secondary HLH is more common in adults and is associated with factors such as infection, tumors, rheumatic diseases, immunotherapy, pregnancy, organ and hematopoietic stem cell transplantation, and metabolic diseases.¹⁴ In adult patients, secondary HLH is life-threatening and has a poor prognosis, and background diseases have the greatest impact on the disease prognosis.¹⁵ Hemophagocytic lymphohistiocytosis secondary to malignant tumors has the worst prognosis,¹⁴ and is mainly treated to deal with the primary tumors.¹⁶ However, many patients often have difficulty tolerating chemotherapy when complicated with HLH, which is one of the reasons for the poor prognosis of tumor-related HLH.¹⁷ Hemophagocytic lymphohistiocytosis induced by Epstein–Barr virus (EBV) infection is the most common non-tumor-related HLH. A clinical study by Zhang et al.¹⁸ found higher EBV DNA load to be an independent poor predictor of OS. Therefore, effective anti-infective therapy is critical for HLH secondary to infection. In a case report by Jongbloed et al.,¹⁹ an adult female patient with HLH secondary to herpes simplex virus 2 infection was successfully treated with acyclovir (for anti-infection), immunoglobulins (for enhancing immunity) and dexamethasone (for anti-inflammation).

In this study, the ORR was higher than 50% in all 3 groups. Although ORR in the JHZ group was higher than in the HZ and JZ groups, the results suggested no significant difference in the efficacy among the 3 groups. Additionally, patients in the JHZ group had better OS and significantly longer median PFS compared with the other 2 groups. Our results are consistent with previous studies. Etoposide induces the normalization of lymphocyte apoptosis,⁷ and dexamethasone has anti-inflammatory effects. The combination of these 2 drugs inhibits the excessive immune response to a certain extent and effectively relieves immune disorders in the body. Supportive therapy, including anti-infection, enhancing immunity and other treatments, is important for the treatment of the primary disease and prolonging OS of patients. Wei et al.²⁰ used etoposide combined with dexamethasone to treat 37 adult patients with secondary HLH, and the results showed that the ORR of the treated cases was as high as 45.9%, which was basically consistent with our results. Yoon et al.²¹ treated 81 adult patients with secondary HLH not associated with malignancy with HLH-94 protocol, 18 with dexamethasone + cyclosporine, and 23 with dexamethasone alone. The results revealed that 43 patients treated with HLH-94 protocol achieved CR at 4 weeks after treatment and 38 patients achieved CR at 8 weeks and later. We believe

that secondary HLH in adults is a disease with complex etiology, diverse clinical manifestations and poor prognosis. Early diagnosis and early treatment are important measures to improve the prognosis, and active treatment is the key to improving the prognosis. Based on the comparison of 3 treatment regimens, a combination of corticosteroids therapy, chemotherapy and supportive therapy showed better clinical benefit for adult secondary HLH than the other 2 treatment regimens, and may be a priority and feasible treatment regimen. Our experience is to use etoposide in combination with glucocorticoids early to control inflammation, and then administer targeted chemotherapy when the condition is stable.

In terms of prognostic factors, Cox regression analysis suggested that age, pathological type (tumor-related and immune disease-related) and hyperbilirubinemia were independent risk factors for OS in adults with secondary HLH. In a clinical study, Trottestam et al.²² found that older patients were more likely to develop secondary HLH after HLH-94 treatment. However, the patients in that study were younger (2–134 months), whereas the present study examined secondary HLH in adults, with a median age exceeding 50 years. In addition, there are no other studies confirming age or pathological type as a prognostic risk factor for secondary HLH in adults. Further multicenter, multi-sample, clinical randomized controlled trials are needed to confirm this. Yoon et al.²¹ also suggested that age and hyperbilirubinemia were associated with poor OS in a multivariate analysis of EBV-HLH subgroups. In the study by Yu et al.,²³ hyperbilirubinemia or jaundice had a significant correlation with adverse outcomes in lymphoma-associated HLH. Cattaneo et al.²⁴ in their multivariate analysis confirmed that HLH patients with hyperbilirubinemia had a higher risk of mortality.

All of the above findings are consistent with our own. Bilirubin is a waste product of heme metabolism in red blood cells, mainly derived from hemoglobin. Hyperbilirubinemia occurs when the liver's capacity to metabolize and convert bilirubin is reduced due to liver injury. This leads to an inadequate elimination of bilirubin from the body, allowing it to accumulate in the blood and ultimately causing a significant increase in blood bilirubin levels.²⁵ Hyperbilirubinemia is extremely harmful to the human body. The accumulation of a substantial amount of bilirubin, which has inherent toxicity, results in severe jaundice and poses a potential life-threatening risk. Therefore, when adult patients with secondary HLH develop hyperbilirubinemia, active treatment should be administered to prolong OS.

Limitations

Due to the limitation of objective conditions such as time constrains, the number of samples in the JHZ group was too small, and more samples should be included for investigation in the future.

Conclusions

Early diagnosis and treatment are important measures to improve the prognosis of adult patients with secondary HLH, a disease with complex etiology, diverse symptoms and poor prognosis. The combination of corticosteroids, chemotherapy and supportive therapies may be the preferred and feasible treatment regimen for this disease. Hyperbilirubinemia can serve as an important indicator to predict the disease prognosis in clinical practice.

Supplementary data

The Supplementary materials are available at <https://doi.org/10.5281/zenodo.10065347>. The package includes the following files:

Supplementary Table 1. Analysis of normal distribution for continuous variable (age).

Supplementary Table 2. Supremum test for proportional hazards assumption

Supplementary Table 3. Tests of non-multicollinearity.

Supplementary Fig. 1. Q-Q figures of the normal distribution analysis of the age values.

Supplementary Fig. 2. The relationship between log-hazard function and age.












Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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