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Clinical features and prognostic impact of hemophagocytic lymphohistiocytosis in angioimmunoblastic T-cell lymphoma: a single-center retrospective study

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Abstract

Background: Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive nodal T-follicular helper-cell lymphoma with prominent immune dysregulation. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome. However, the clinical characteristics and prognostic impact of AITL-associated HLH (AITL-HLH) remain unclear.

Methods: We retrospectively analyzed 70 consecutive patients with AITL diagnosed between January 2015 and January 2025. Clinical features, laboratory findings, treatment regimens, and outcomes were compared according to HLH status.

Results: Of the 70 patients, 23 (32.9%) developed AITL-HLH,5 (21.7%) before AITL diagnosis, 9 (39.1%) synchronously, and 9 (39.1%) more than 30 days after AITL diagnosis. Compared with patients without HLH, those with HLH more frequently had fever, B symptoms, Ann Arbor stage IV disease, bone-marrow hemophagocytosis, anemia, thrombocytopenia, hypoalbuminemia, hyperferritinemia, and peripheral-blood EBV-DNA positivity ($P < 0.05$). Median overall survival (19.2 vs 46.1 months; $P = 0.037$) and progression-free survival (9.6 vs 31.6 months; $P = 0.038$) were shorter in the HLH group, whereas lymphoma response rates were similar. Multivariable analysis identified poorer Eastern Cooperative Oncology Group performance status (HR 2.31; $P = 0.038$), higher direct bilirubin (HR 1.03 per 1 μmol/L; $P < 0.001$), and lower platelet count (HR 0.95 per 10×10^9/L; $P = 0.021$) as independent adverse factors.

Conclusions: AITL-HLH is an aggressive and temporally heterogeneous inflammatory phenotype. Peripheral-blood EBV-DNA positivity, rather than quantitative viral burden, was associated with HLH. A favorable short-term response of HLH does not necessarily translate into prolonged survival. Early recognition and prompt control of hyperinflammation and lymphoma are essential.

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare mature T-cell lymphoma that originates from T-follicular helper (TFH) cells, accounting for approximately 1–2% of all non-Hodgkin lymphomas worldwide and 15–20% of peripheral T-cell lymphomas [1, 2]. AITL primarily affects older adults and typically presents with generalized lymphadenopathy, B symptoms, hepatosplenomegaly, and advanced-stage disease [3]. Despite intensive treatment, the prognosis remains poor, with a median overall survival (OS) of approximately 2–3 years [4, 5].

Hemophagocytic syndrome, also known as hemophagocytic lymphohistiocytosis (HLH), is a life-threatening disorder caused by immune dysregulation and characterized by a hyperinflammatory cytokine storm [6]. Excessive activation of monocytes and macrophages and overproduction of inflammatory cytokines can lead to fever, cytopenias, hepatosplenomegaly, and hemophagocytosis in the bone marrow, liver, lymph nodes, or other tissues. HLH is classified as primary or secondary according to its underlying causes [6].

Lymphoma is one of the most common triggers of secondary HLH in adults. T-cell and natural killer (NK)-cell lymphomas are frequent causes of lymphoma-associated HLH (LA-HLH), accounting for approximately 35% of cases [7]. In a scoping review of 132 articles involving 542 patients with LA-HLH, Knauft et al. reported that T-cell and B-cell non-Hodgkin lymphomas accounted for 45.2% and 45.6% of cases, respectively, and that AITL accounted for 6.1% of T-cell non-Hodgkin lymphoma-associated HLH [8]. The review also suggested that AITL-HLH is one of the poorest prognosis subtypes compared to other subtypes of LA-HLH [8].

AITL has a biological basis for immune activation because of its TFH-cell origin, cytokine-rich microenvironment, expansion of Epstein-Barr virus (EBV)-positive reactive B cells, and autoimmune features. However, published evidence on AITL-associated HLH consists mainly of case reports or small subsets within broader LA-HLH cohorts [9–15]. The temporal relationship between HLH and AITL diagnosis, the clinical and laboratory differences between AITL-HLH and AITL without HLH, and the impact of HLH on treatment and survival remain to be clarified.

Patients and methods

Study design and patients

We retrospectively analyzed 70 consecutive patients with histopathologically confirmed AITL diagnosed at Beijing Friendship Hospital between January 2015 and January 2025. Of these, 47 did not develop HLH and 23 developed AITL-HLH. Patients were followed until December 2025 or death. The median follow-up was 44.8 months (interquartile range [IQR], 28.2–89.1 months). AITL was diagnosed according to the World Health Organization classification [16], and HLH was diagnosed according to the HLH-2004 criteria [17].

Data collection and definitions

Collected variables included age, sex, fever, B symptoms, splenomegaly, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor stage, International Prognostic Index (IPI), bone-marrow involvement, hemophagocytosis, EBV-encoded RNA (EBER), peripheral-blood EBV-DNA status, plasma and peripheral-blood mononuclear-cell (PBMC) EBV-DNA loads, EBV-infected lymphocyte subset, Ki-67 index, complete blood count, hepatic and renal function, lactate dehydrogenase (LDH), β2-microglobulin, triglycerides, fibrinogen, ferritin, treatment regimen, response, transplantation status, survival status, and cause of death. For patients with HLH, soluble CD25 (sCD25) levels and NK-cell activity were assessed. These dates were collected at the date of pathological AITL diagnosis and before initiation of lymphoma directed therapy. For patients with HLH, HLH-related dates were recorded at the time of HLH diagnosis and before HLH-directed therapy whenever available.

The temporal relationship between AITL and HLH was determined by the interval between the pathological diagnosis of AITL and the diagnosis of HLH. HLH diagnosed more than 30 days before AITL

was defined as pre-AITL HLH; HLH diagnosed within 30 days before or after AITL diagnosis was defined as synchronous HLH; and HLH diagnosed more than 30 days after AITL diagnosis was defined as post-AITL HLH. OS was defined as the time from AITL diagnosis to death from any cause or last follow-up. Progression-free survival (PFS) was defined as the time from diagnosis of AITL to the first documented lymphoma progression, relapse, or death from any cause, whichever occurred first; patients without progression, relapse, or death were censored at last follow-up.

Treatment and response assessment

HLH-directed therapy was categorized as DEP (liposomal doxorubicin, etoposide, and methylprednisolone), glucocorticoid- and/or ruxolitinib-based non-DEP therapy, CHOP-like therapy used to control both AITL and HLH, or other individualized treatment. AITL-directed frontline treatment was categorized as CHOP/CHOP-like therapy, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (BV-CHP), or other individualized systemic regimens. Salvage therapy and hematopoietic stem cell transplantation (HSCT) were recorded separately.

AITL responses, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), were evaluated according to the revised response criteria of Cheson et al. [18]. HLH responses, including CR, PR, and no response (NR), were assessed using the criteria proposed by Marsh et al., with modifications based on our research group's experience [19, 20]. Best overall response (BOR) was defined as the best documented response achieved before disease progression or treatment change. The overall response rate (ORR) was defined as CR plus PR, and the disease control rate (DCR) as CR plus PR plus SD.

Statistical analysis

Continuous variables with a normal distribution are presented as mean ± standard deviation (SD) and were compared using the independent-samples Student's t-test. Non-normally distributed continuous variables are presented as median (IQR) and were compared using the Mann-Whitney U test. Categorical variables are presented as frequencies and percentages, n (%), and were compared using the chi-square test or Fisher's exact test, as appropriate.

Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Associations between clinical or laboratory variables and OS were evaluated using Cox proportional hazards regression models. Univariate Cox regression analyses were first performed for all candidate variables, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated. Variables with $P < 0.05$ in the univariate analysis were subsequently entered into the multivariable Cox proportional hazards model. An $HR > 1$ indicated an increased risk of death, whereas an $HR < 1$ indicated a reduced risk.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R software (version ≥ 4.0).

Results

Baseline clinical characteristics according to HLH status

The cohort included 70 patients with AITL; 23 (32.9%) had AITL-associated HLH and 47 (67.1%) did not. The mean age was 59.54 ± 11.00 years, and 47 patients (67.1%) were male.

Patients with AITL-HLH showed a more inflammatory and clinically advanced phenotype. Fever was observed in 91.3% of patients with HLH and 44.7% of those without HLH ($P < 0.001$). B symptoms were more frequent in the HLH group (87.0% vs 57.4%; $P = 0.014$), as was Ann Arbor stage IV disease (73.9% vs 44.7%; $P = 0.021$). Peripheral-blood EBV-DNA positivity was also more frequent in the HLH group than in the non-HLH group (82.6% vs 51.1%; $P = 0.037$) (Table 1).

Table 1
Clinical characteristics of patients with AITL according to HLH status

Characteristic	Total (n = 70)	Non-HLH (n = 47)	AITL-HLH (n = 23)	P value
Sex, n (%)				**0.054**
Male	47 (67.1)	28 (59.6)	19 (82.6)	
Female	23 (32.9)	19 (40.4)	4 (17.4)	
Age, years, mean ± SD	59.54 ± 11.00	60.47 ± 10.84	57.65 ± 11.32	0.318
Ann Arbor stage, n (%)				**0.021**
II-III	32 (45.7)	26 (55.3)	6 (26.1)	
IV	38 (54.3)	21 (44.7)	17 (73.9)	
B symptoms, n (%)				**0.014**
Yes	47 (67.1)	27 (57.4)	20 (87.0)	
No	23 (32.9)	20 (42.6)	3 (13.0)	
IPI score, n (%)				**0.291**
0–2	21 (30.0)	16 (34.0)	5 (21.7)	
3–5	49 (70.0)	31 (66.0)	18 (78.3)	
IPI risk category, n (%)				**0.295**
Low-intermediate	21 (30.0)	16 (34.0)	5 (21.7)	
Intermediate-high	49 (70.0)	31 (66.0)	18 (78.3)	
ECOG performance status, n (%)				**0.187**
ECOG 0–1	59 (84.3)	42 (89.4)	17 (73.9)	
ECOG 2–3	11 (15.7)	5 (10.6)	6 (26.1)	
Fever, n (%)				**< 0.001**
No	28 (40.0)	26 (55.3)	2 (8.7)	
Yes	42 (60.0)	21 (44.7)	21 (91.3)	
Splenomegaly, n (%)				**0.555**

Note: Data are presented as n (%), mean ± SD, or median (IQR), as indicated. Missing indicates unavailable data; transplantation type was unknown for two patients. AITL, angioimmunoblastic T-cell lymphoma; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HSCT, hematopoietic stem cell transplantation.

Characteristic	Total (n = 70)	Non-HLH (n = 47)	AITL-HLH (n = 23)	P value
Sex, n (%)				**0.054**
No	37 (52.9)	26 (55.3)	11 (47.8)	
Yes	33 (47.1)	21 (44.7)	12 (52.2)	
Hemophagocytosis, n (%)				**< 0.001**
No	55 (78.6)	45 (95.7)	10 (43.5)	
Yes	12 (17.1)	0 (0.0)	12 (52.2)	
Missing	3 (4.3)	2 (4.3)	1 (4.3)	
Bone marrow involvement, n (%)				**0.257**
No	46 (65.7)	33 (70.2)	13 (56.5)	
Yes	24 (34.3)	14 (29.8)	10 (43.5)	
Ki-67 index, %, median (IQR)	40.00 (40.00, 50.00)	40.00 (40.00, 50.00)	50.00 (40.00, 60.00)	0.058
Peripheral-blood EBV DNA, n (%)				**0.037**
Negative	18 (25.7)	15 (31.9)	3 (13.0)	
Positive	43 (61.4)	24 (51.1)	19 (82.6)	
Missing	9 (12.9)	8 (17.0)	1 (4.3)	
EBER, n (%)				**0.147**
Negative	19 (27.1)	16 (34.0)	3 (13.0)	
Positive	47 (67.1)	28 (59.6)	19 (82.6)	
Missing	4 (5.7)	3 (6.4)	1 (4.3)	
HSCT type among patients with known type, n (%)				**1.000**
Autologous HSCT	5 (62.5)	4 (66.7)	1 (50.0)	
Allogeneic HSCT	3 (37.5)	2 (33.3)	1 (50.0)	

Note: Data are presented as n (%), mean ± SD, or median (IQR), as indicated. Missing indicates unavailable data; transplantation type was unknown for two patients. AITL, angioimmunoblastic T-cell lymphoma; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HSCT, hematopoietic stem cell transplantation.

Laboratory findings according to HLH status

Compared with patients without HLH, those with AITL-HLH had lower hemoglobin levels ($P < 0.001$), lower platelet counts ($P = 0.009$), lower albumin levels ($P = 0.024$), and higher ferritin levels ($P = 0.002$) (Table 2).

Table 2
Laboratory findings of patients with AITL according to HLH status

Variable	Total (n = 70)	Non-HLH (n = 47)	AITL-HLH (n = 23)	P value
WBC, × 10⁹/L, median (IQR) [3.5–9.5]	5.87 (4.40, 9.92)	5.79 (4.50, 8.14)	5.94 (3.26, 13.05)	0.783
ANC, × 10⁹/L, median (IQR) [1.8–6.3]	4.17 (2.96, 5.88)	4.11 (2.97, 5.52)	4.26 (2.98, 9.23)	0.512
HGB, g/L, mean ± SD [130–175]	102.91 ± 24.88	110.53 ± 22.33	87.35 ± 22.85	< 0.001
PLT, × 10⁹/L, median (IQR) [125–350]	165.50 (88.25, 221.25)	180.00 (128.50, 235.50)	88.00 (44.50, 168.00)	0.009
ALT, U/L, median (IQR) [7.0–44.0]	17.50 (12.25, 27.50)	17.00 (12.00, 24.50)	20.00 (14.50, 30.50)	0.141
AST, U/L, median (IQR) [13.0–35.0]	19.15 (14.30, 30.00)	18.70 (14.95, 24.25)	19.30 (13.90, 38.75)	0.726
ALB, g/L, median (IQR) [40–55]	33.60 (30.13, 36.85)	34.20 (31.55, 37.60)	31.70 (27.10, 34.70)	0.024
LDH, U/L, median (IQR) [120–250]	263.00 (199.25, 361.00)	272.00 (198.50, 377.00)	262.00 (217.00, 322.00)	0.569
β2-microglobulin, mg/L, median (IQR) [1.09–2.53]	3.85 (2.89, 6.02)	4.58 (2.96, 6.01)	3.37 (2.88, 5.66)	0.591
TBIL, μmol/L, median (IQR) [3.42-21.00]	12.45 (9.82, 17.11)	13.16 (9.78, 16.06)	11.44 (9.86, 18.58)	0.653
DBIL, μmol/L, median (IQR) [0.00-6.84]	4.46 (3.46, 6.89)	4.33 (3.34, 6.29)	4.77 (3.95, 7.06)	0.294
Creatinine, μmol/L, median (IQR) [41.0-111.0]	66.25 (55.55, 81.28)	67.80 (60.60, 87.30)	61.00 (49.95, 76.80)	0.074
TG, mmol/L, median (IQR) [0.57–1.70]	1.76 (1.34, 2.16)	1.75 (1.24, 2.03)	1.85 (1.58, 2.57)	0.075
Fibrinogen, g/L, median (IQR) [2–4]	2.70 (2.10, 3.84)	2.85 (2.24, 3.79)	2.10 (1.48, 3.51)	0.065
Ferritin, ng/mL, median (IQR) [24.00-336.00]	509.00 (338.65, 1376.70)	354.00 (183.40, 799.40)	1040.90 (444.75, 1426.72)	0.002

Note: Data are presented as mean ± SD or median (IQR), unless otherwise indicated; reference intervals are shown in brackets. WBC, white blood cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin; TG, triglycerides; PBMC, peripheral-blood mononuclear cells; EBV, Epstein-Barr virus; NK, natural killer.

Variable	Total (n = 70)	Non-HLH (n = 47)	AITL-HLH (n = 23)	P value
Plasma EBV-DNA load, copies/mL, median (IQR)	5600.00 (650.00, 20000.00)	6600.00 (900.00, 32000.00)	4405.00 (717.50, 9425.00)	0.543
PBMC EBV-DNA load, copies/mL, median (IQR)	19180.00 (2000.00, 333000.00)	19090.00 (1900.00, 127000.00)	35000.00 (6700.00, 1028500.00)	

Note: Data are presented as mean ± SD or median (IQR), unless otherwise indicated; reference intervals are shown in brackets. WBC, white blood cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin; TG, triglycerides; PBMC, peripheral-blood mononuclear cells; EBV, Epstein-Barr virus; NK, natural killer.

Temporal relationship between HLH and AITL

Synchronous HLH was defined as HLH diagnosed within 30 days before or after AITL diagnosis. Among the 23 patients with AITL-HLH, HLH preceded AITL diagnosis by more than 30 days in 5 (21.7%), occurred synchronously in 9 (39.1%), and developed more than 30 days after AITL diagnosis in 9 (39.1%). Among patients with pre-AITL HLH, the median interval from HLH diagnosis to AITL diagnosis was 3.7 months (range, 1.1–6.5 months). Among patients with post-AITL HLH, the median interval from AITL diagnosis to HLH development was 7.1 months (range, 1.0-16.2 months).

Treatment patterns and response assessment

AITL-directed therapy was administered to 64 patients (91.4%), including 43 patients without HLH (91.5%) and 21 with HLH (91.3%). CHOP/CHOP-like therapy was the most commonly used frontline regimen overall, but it was less frequently used in the HLH group than in the non-HLH group (47.8% vs 76.6%; P = 0.029). BV-CHP and other individualized regimens were more common in the HLH group. 10 patients underwent HSCT, including 8 without HLH and 2 with HLH. 5 patients received autologous HSCT, 3 received allogeneic HSCT, and the transplantation type was unknown for 2 patients.

52 patients were evaluable for BOR, including 11 (21.2%) with CR, 22 (42.3%) with PR, 8 (15.4%) with SD, and 11 (21.2%) with PD. The BOR distribution did not differ significantly between the HLH and non-HLH groups (P = 0.949). The overall ORR was 63.5%, with similar rates in the HLH and non-HLH groups (64.7% vs 62.9%; P = 0.897). The DCR was also comparable between groups (76.5% vs 80.0%; P = 1.000). Among the 23 patients with AITL-HLH, 21 had documented HLH-directed therapy, most commonly DEP-containing regimens. 20 patients were evaluable for HLH response: 1 achieved CR, 15 achieved PR, and 4 had NR, yielding an HLH ORR of 80.0% (Table 3).

Table 3
Treatment patterns and response outcomes according to HLH status

Treatment or response	Total	Non-HLH	AITL-HLH	P value
AITL-directed therapy	64/70 (91.4%)	43/47 (91.5%)	21/23 (91.3%)	1.000
First-line CHOP/CHOP-like regimen	47/70 (67.1%)	36/47 (76.6%)	11/23 (47.8%)	0.029
First-line BV-CHP	4/70 (5.7%)	1/47 (2.1%)	3/23 (13.0%)	0.100
Other first-line regimen	13/70 (18.6%)	6/47 (12.8%)	7/23 (30.4%)	0.103
Received salvage therapy	33/70 (47.1%)	22/47 (46.8%)	11/23 (47.8%)	1.000
Underwent HSCT	10/70 (14.3%)	8/47 (17.0%)	2/23 (8.7%)	0.480
Best overall response evaluable	52/70 (74.3%)	35/47 (74.5%)	17/23 (73.9%)	
BOR: CR, among evaluable	11/52 (21.2%)	7/35 (20.0%)	4/17 (23.5%)	
BOR: PR, among evaluable	22/52 (42.3%)	15/35 (42.9%)	7/17 (41.2%)	
BOR: SD, among evaluable	8/52 (15.4%)	6/35 (17.1%)	2/17 (11.8%)	
BOR: PD, among evaluable	11/52 (21.2%)	7/35 (20.0%)	4/17 (23.5%)	0.949
ORR (CR + PR), among evaluable	33/52 (63.5%)	22/35 (62.9%)	11/17 (64.7%)	0.897
DCR (CR + PR+SD), among evaluable	41/52 (78.8%)	28/35 (80.0%)	13/17 (76.5%)	1.000
HLH-directed therapy documented	NA	NA	21/23 (91.3%)	
DEP regimen	NA	NA	13/23 (56.5%)	

Note: Values are n/N (%). BOR, best overall response; BV-CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin/epirubicin, vincristine, and prednisone; DEP, liposomal doxorubicin, etoposide, and methylprednisolone; CR, complete response; DCR, disease control rate; HSCT, hematopoietic stem cell transplantation; NA, not applicable; NR, no response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Treatment or response	Total	Non-HLH	AITL-HLH	P value
Glucocorticoid/ruxolitinib-based regimen	NA	NA	3/23 (13.0%)	
CHOP-like regimen used as HLH-directed therapy	NA	NA	3/23 (13.0%)	
Other HLH-directed treatment	NA	NA	2/23 (8.7%)	
HLH response evaluable	NA	NA	20/23 (87.0%)	
HLH CR	NA	NA	1/20 (5.0%)	
HLH PR	NA	NA	15/20 (75.0%)	
HLH ORR (CR + PR)	NA	NA	16/20 (80.0%)	
HLH NR	NA	NA	4/20 (20.0%)	

Note: Values are n/N (%). BOR, best overall response; BV-CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin/epirubicin, vincristine, and prednisone; DEP, liposomal doxorubicin, etoposide, and methylprednisolone; CR, complete response; DCR, disease control rate; HSCT, hematopoietic stem cell transplantation; NA, not applicable; NR, no response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Survival outcomes and prognostic factors

Kaplan-Meier survival analysis was performed for all 70 patients. During follow-up, the median OS for the entire cohort was 42.6 months (95% CI, 21.8 months to not reached). The estimated 1-, 3-, and 5-year OS rates were 73.8%, 52.0%, and 40.5%, respectively (Fig. 1a). The median OS was 19.2 months (95% CI, 4.4 months to not reached) in the HLH group and 46.1 months (95% CI, 29.7 months to not reached) in the non-HLH group. HLH was associated with a significantly increased risk of death (HR 2.18, 95% CI 1.03–4.62; log-rank P = 0.037) (Fig. 1b). The estimated 1-, 3-, and 5-year OS rates were 50.9%, 36.3%, and 36.3%, respectively, in the HLH group, compared with 82.7%, 58.7%, and 44.9% in the non-HLH group.

A total of 41 PFS events were observed, including lymphoma progression, relapse, or death. The median PFS of the entire cohort was 17.7 months. Patients with AITL-HLH had significantly shorter PFS than those without HLH (median, 9.6 vs 31.6 months; HR 1.97, 95% CI 1.03–3.77; log-rank P = 0.038) (Fig. 2).

Univariate and multivariable Cox regression analyses are shown in Table 4. In univariate analysis, AITL-HLH (HR 2.18, 95% CI 1.03–4.62; P = 0.042), higher IPI score (HR 2.39, 95% CI 1.03–5.58; P = 0.043), higher IPI risk category (HR 2.39, 95% CI 1.03–5.58; P = 0.043), poorer ECOG performance status (HR 2.72, 95% CI 1.25–5.92; P = 0.012), fever (HR 2.30, 95% CI 1.08–4.89; P = 0.031), higher direct bilirubin (DBIL; HR 1.02, 95% CI 1.01–1.04; P = 0.002), and lower platelet count (PLT; HR 0.95, 95% CI 0.91–0.99;

P = 0.015) were associated with inferior OS. In multivariable analysis, poorer ECOG performance status (HR 2.31, 95% CI 1.05–5.11; P = 0.038), higher DBIL (HR 1.03, 95% CI 1.01–1.05; P < 0.001), and lower PLT (HR 0.95, 95% CI 0.91–0.99; P = 0.021) remained independently associated with inferior OS.

Table 4
Cox regression analysis of prognostic factors for overall survival in patients with AITL

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
HLH status				
No HLH	Ref.			
HLH	2.18 (1.03–4.62)	0.042		
Sex				
Male	Ref.			
Female	0.56 (0.25–1.25)	0.158		
Age	1.02 (0.99–1.05)	0.283		
Ann Arbor stage				
II-III	Ref.			
IV	1.83 (0.90–3.72)	0.097		
IPI score				
0–2	Ref.			
3–5	2.39 (1.03–5.58)	0.043		
B symptoms				
No	Ref.			
Yes	1.55 (0.73–3.28)	0.254		
IPI risk category				
Low-intermediate	Ref.			
Intermediate-high	2.39 (1.03–5.58)	0.043		
ECOG performance status				
0–1	Ref.		Ref.	

Note: PLT was modeled per 10 × 10⁹/L increase; DBIL was modeled per 1 μmol/L increase. CI, confidence interval; HR, hazard ratio; WBC, white blood cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; DBIL, direct bilirubin; Cr, creatinine; TG, triglycerides; Fbg, fibrinogen; sCD25, soluble CD25; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HSCT, hematopoietic stem cell transplantation; Ref, reference.

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
HLH status				
2–3	2.72 (1.25–5.92)	0.012	2.31 (1.05–5.11)	0.038
Fever				
No	Ref.			
Yes	2.30 (1.08–4.89)	0.031		
Splenomegaly				
No	Ref.			
Yes	0.90 (0.45–1.80)	0.759		
WBC	0.98 (0.92–1.04)	0.511		
ANC	0.95 (0.87–1.04)	0.288		
HGB	0.99 (0.97–1.00)	0.067		
PLT	0.95 (0.91–0.99)	0.015	0.95 (0.91–0.99)	0.021
ALT	1.01 (0.99–1.03)	0.229		
AST	1.01 (0.99–1.03)	0.348		
ALB	1.00 (0.95–1.05)	0.910		
LDH	1.00 (1.00–1.00)	0.841		
β2-microglobulin	1.10 (0.99–1.22)	0.067		
DBIL	1.02 (1.01–1.04)	0.002	1.03 (1.01–1.05)	< 0.001
Cr	1.01 (1.00–1.01)	0.172		
TG	1.15 (0.82–1.63)	0.415		
Fbg	0.88 (0.65–1.20)	0.419		
Bone marrow involvement				
No	Ref.			

Note: PLT was modeled per 10 × 10^9/L increase; DBIL was modeled per 1 μmol/L increase. CI, confidence interval; HR, hazard ratio; WBC, white blood cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; DBIL, direct bilirubin; Cr, creatinine; TG, triglycerides; Fbg, fibrinogen; sCD25, soluble CD25; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HSCT, hematopoietic stem cell transplantation; Ref, reference.

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
HLH status				
Yes	1.54 (0.73–3.23)	0.254		
Ki-67 index (%)	1.01 (0.98–1.05)	0.359		
sCD25/ferritin ratio	1.00 (1.00–1.00)	0.802		
Peripheral-blood EBV DNA				
Negative	Ref.			
Positive	1.03 (0.48–2.23)	0.934		
Missing	0.60 (0.17–2.20)	0.443		
EBER				
Negative	Ref.			
Positive	1.05 (0.49–2.27)	0.901		
Missing	1.47 (0.40–5.37)	0.557		
HSCT				
No	Ref.			
Yes	0.51 (0.16–1.69)	0.274		

Note: PLT was modeled per 10 × 10⁹/L increase; DBIL was modeled per 1 μmol/L increase. CI, confidence interval; HR, hazard ratio; WBC, white blood cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; DBIL, direct bilirubin; Cr, creatinine; TG, triglycerides; Fbg, fibrinogen; sCD25, soluble CD25; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein-Barr virus; EBER, EBV-encoded RNA; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HSCT, hematopoietic stem cell transplantation; Ref, reference.

Discussion

Lymphoma-associated hemophagocytic lymphohistiocytosis is an important form of malignancy-associated HLH in adults and is usually associated with rapid clinical deterioration and poor survival [7, 8, 21]. AITL originates from T-follicular helper cells and is characterized by marked immune dysregulation, abnormal cytokine signaling, and expansion of EBV-positive reactive B cells [2, 22]. These biological features may contribute to the development of excessive immune activation and HLH. However, the frequency of HLH in patients with AITL has not been well established. Xie et al. reported HLH at presentation in 3 of 21 patients with AITL, whereas another study of T/NK-cell lymphomas identified HLH in only 2 of 89 patients with AITL [23, 24]. In our cohort, 23 of 70 patients developed HLH

during the disease course, corresponding to a frequency of 32.9%. The main reason for this high incidence is maybe that our center has been focusing on HLH diagnosis and treatment.

Of the 23 patients with AITL-HLH in our study, HLH preceded AITL diagnosis in 5 (21.7%), occurred synchronously in 9 (39.1%), and developed more than 30 days after AITL diagnosis in 9 (39.1%); the median interval in the latter group was 7.1 months, while in the pre-AITL group was 3.7 months. Previous LA-HLH cohorts have shown that HLH may occur at lymphoma presentation or develop during treatment, progression, or relapse [14, 21, 25]. Therefore, in adult patients with HLH of unknown cause, the possibility of an underlying lymphoma should be considered, especially in the presence of lymphadenopathy, B symptoms, or persistent EBV DNA positive in blood. When the first pathological examination cannot explain the clinical manifestations, repeat lymph-node biopsy may be necessary [14, 21, 26].

In our study, we found that patients with AITL-HLH had more severe clinical and laboratory abnormalities than patients without HLH. Fever, B symptoms, Ann Arbor stage IV disease, bone-marrow hemophagocytosis, anemia, thrombocytopenia, hypoalbuminemia, and hyperferritinemia were more common in the HLH group. These findings are consistent with those reported in previous studies. For example, Xie et al. compared the clinical characteristics, treatments, and prognosis of aggressive peripheral T cell lymphoma (PTCL) patients with and without HLH. They found that the HLH group had higher serum β2-microglobulin, ferritin, triglycerides, and hypofibrinogen levels, and so were bone marrow involvement, liver dysfunction, hepatosplenomegaly, and B symptoms [23]. Tong et al. reviewed 173 PTCL patients and found that 64% AITL patients had bone marrow involvement (BMI). In the BMI group, 36% patients progressed to LA-HLH. High ferritin level and liver dysfunction were also more common in the BMI group [27]. These findings suggest that AITL-HLH is associated with a stronger systemic inflammatory response and more impaired hematopoietic and organ function. Thus, for AITL patients with advanced clinical stage and laboratory abnormalities suggestive of hyperinflammation, we recommended prompt and comprehensive evaluation for HLH, and the possibility of AITL-HLH should be carefully considered.

The association between EBV and AITL-HLH remains unclear. Previous studies have shown that EBER-positive cells are detected in approximately two thirds to three quarters of AITL tissues and are usually located in reactive, non-neoplastic B cells [28]. In our study, there was no significant difference in tissue EBER positivity between the two groups. However, peripheral-blood EBV DNA was detected in 61.4% of the overall cohort, with positivity rates of 59.6% in the non-HLH group and 82.6% in the HLH group. Peripheral-blood EBV DNA positivity was more frequent in patients with HLH than in those without HLH. Zhong et al. conducted a multicenter retrospective study about whole blood EBV DNA state in 323 AITL patients, they pointed that AITL patients with EBV DNA positivity exhibited higher LDH, β2-MG, CRP, and reduced albumin levels compared to EBV DNA negative cases. Additionally, EBV DNA positive status correlated with poorer ECOG, increased bone marrow involvement, and higher-risk prognostic scores [29]. This finding suggesting that peripheral EBV may reflect greater tumor burden, more severe systemic inflammation, and more profound immune dysregulation in AITL. In contrast, Chen et al. studied 26 AITL

patients and found that 88% EBV-positive in tissue specimens. These EBV-positive cells were confined to background B cells rather than the neoplastic T cells of AITL. Notably, hemophagocytosis was less frequent in patients with tissue EBV-positive AITL than in those with EBV-negative patients [30]. These inconsistent findings may be attributable to differences in EBV detection methods, the cellular localization of EBV, and the characteristics of the study populations. Our findings suggest that peripheral-blood EBV DNA positivity may be associated with the development of HLH in patients with AITL. Further studies involving larger cohorts and precise identification of the EBV-infected cell types are needed to validate this association.

Among patients with evaluable HLH responses, the HLH ORR was 80.0%. Lymphoma ORR and DCR were also similar between the HLH and non-HLH groups. Nevertheless, patients with AITL-HLH had significantly shorter PFS and OS. Median PFS was 9.6 months in the HLH group and 31.6 months in the non-HLH group, while median OS was 19.2 and 46.1 months, respectively. Pi et al. conducted a multicenter study of LA-HLH, showed the modified DEP regimen achieved a 4-week ORR of 89.3%; however, the 1-year OS rate was only 34.5%, with a median survival of 6.5 months. These findings suggest that a favorable short-term response of HLH does not necessarily translate into prolonged survival [31]. In our study, poorer ECOG performance status, higher DBIL and lower platelet count were independently associated with inferior OS. Thus, for patients with poor performance status, hyperbilirubinemia, or severe thrombocytopenia may require closer monitoring, rapid control of hyperinflammation, active management of organ dysfunction, and individualized adjustment of treatment intensity.

This was a single-center retrospective study with a limited number of AITL-HLH cases. Treatment was heterogeneous, response assessments were unavailable for some patients, and residual confounding by other risk factors cannot be excluded. EBV analyses were also limited by incomplete quantitative testing. Nonetheless, this study provides a clinically relevant description of the characteristics and prognosis of this uncommon disease.

Conclusion

AITL- HLH represents a temporally heterogeneous, highly inflammatory phenotype associated with adverse clinical outcomes. Peripheral-blood EBV-DNA positivity maybe associated with HLH. Early recognition and prompt control of hyperinflammation and lymphoma are essential.

Statements and Declarations

Author contributions

Xiaodan He collected and analyzed the data and drafted the manuscript. Jingwei Cao collected and analyzed the data. Xiao dan He and Jingwei Cao contributed equally to this work. Gaochao Zhang participated in the design of the study. Yali Du, Shu Fang, Jing Wang, Miao Wang, and Mengyuan Zhou

contributed to data collection. Jingshi Wang designed the study and supervised the research. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval

The study was reviewed and approved by the Ethics Committee of Beijing Friendship Hospital.

Consent to participate

Written informed consent was not required in accordance with national legislation and institutional requirements.

Data availability

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

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Figures

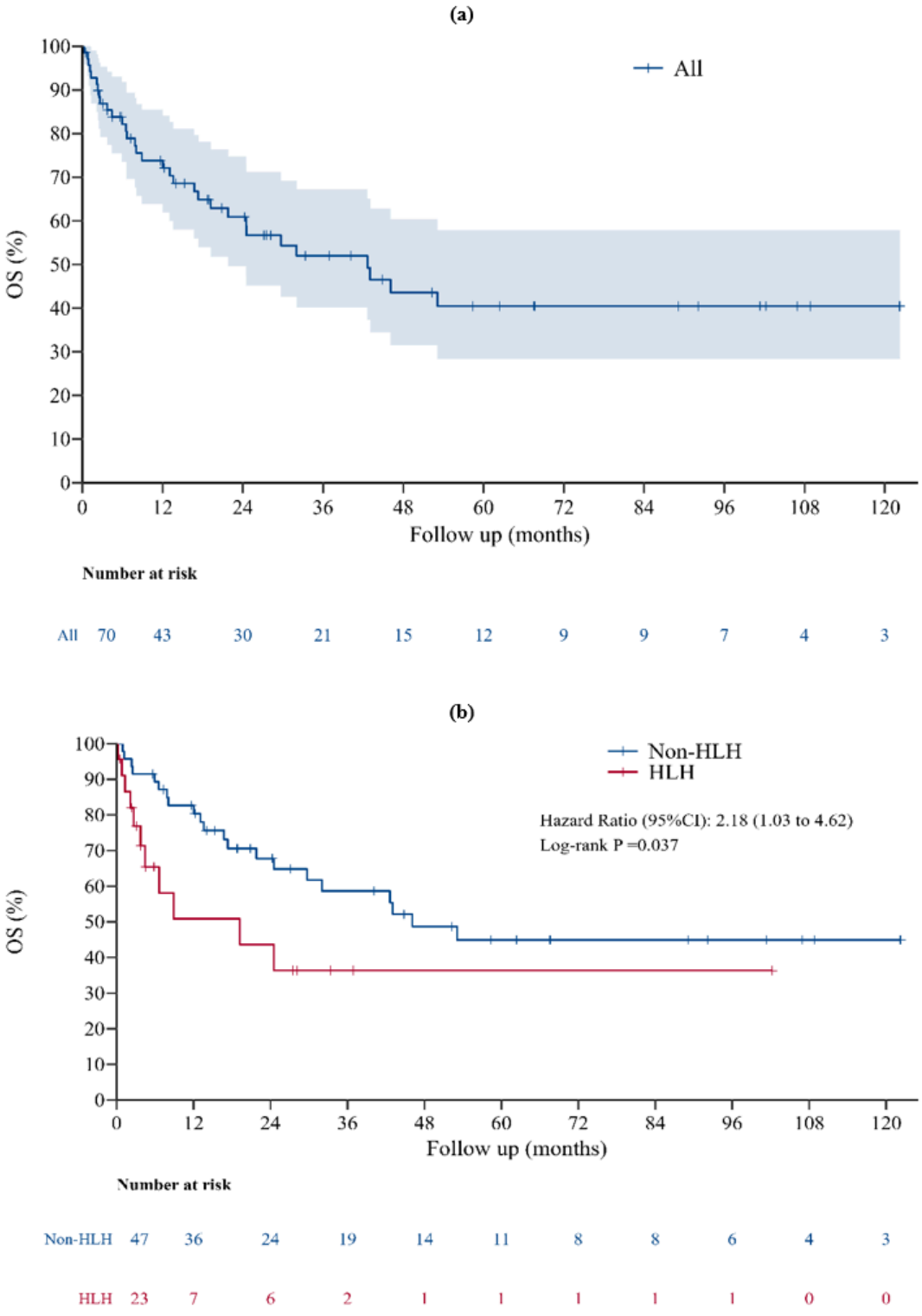


Figure 1

Kaplan-Meier analyses of overall survival (OS) in patients with angioimmunoblastic T-cell lymphoma. a OS in the entire cohort. b Comparison of OS between patients with and without hemophagocytic lymphohistiocytosis.

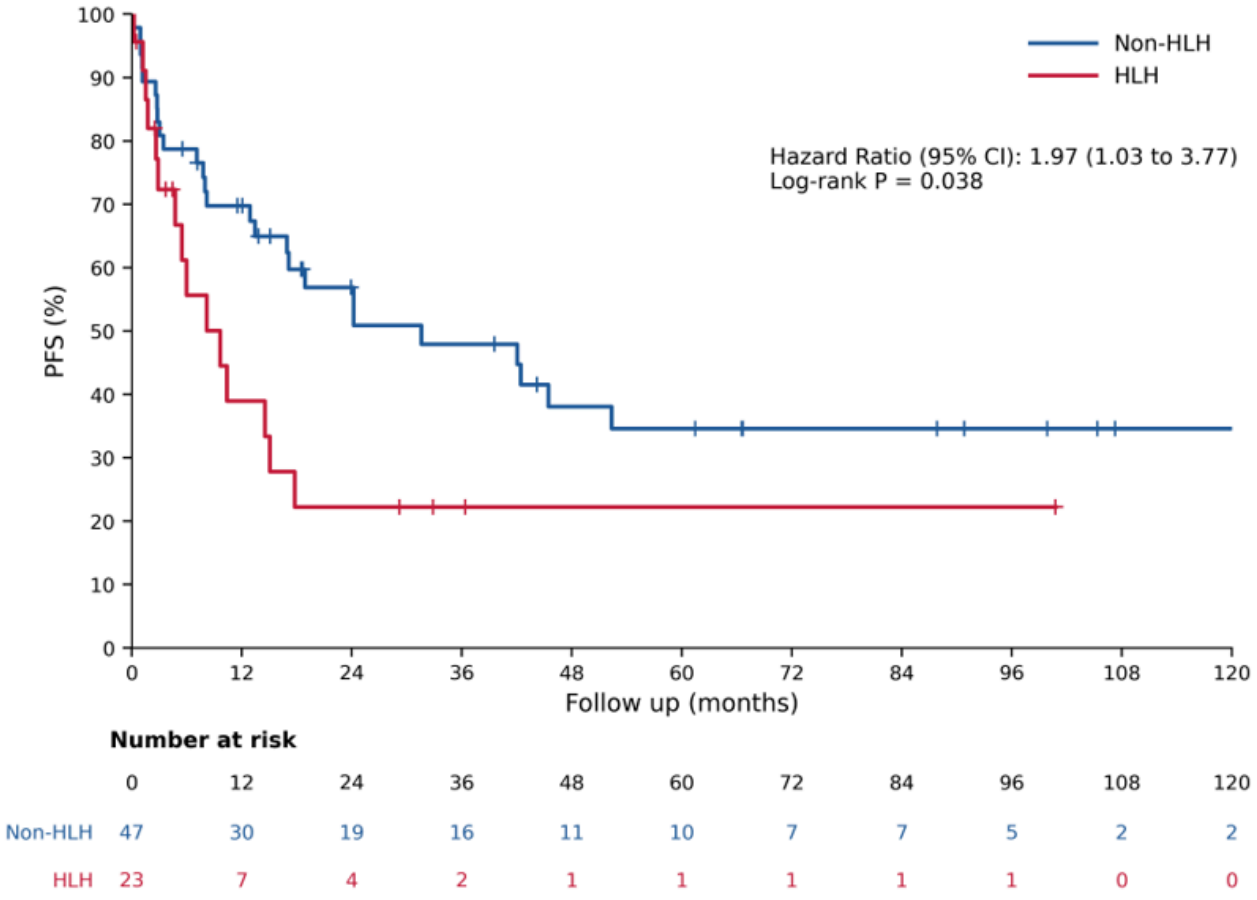


Figure 2

Comparison of progression-free survival (PFS) between patients with angioimmunoblastic T-cell lymphoma with and without hemophagocytic lymphohistiocytosis.