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Original Article

Clinical characteristics and prognosis of lymphoma-associated hemophagocytic syndrome: a retrospective study of 67 adult Chinese patients

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Abstract: Objective: This study aims to identify the clinical and laboratory features of LAHS and clarify the prognostic factors of HLH. Methods: 67 HLH patients were enrolled. 37 LAHS patients and 30 non-LAHS patients were compared. The diagnostic values of F-18 FDG PET/CT and serum ferritin (SF) levels for distinguishing LAHS from HLH were assessed. The survival data and prognostic significance of PET/CT SUVmax value, SF levels and age in the LAHS group were evaluated. Results: Most LAHS patients had remittent fever with unresponsive to antipyretic drugs and weight loss within six months compared to non-LASH patients (62.16% versus 26.67%, $P = 0.0018$). The SF levels and PET/CT SUVmax value in LAHS group were significantly higher than those in non-LAHS group (2000 μg/L versus 632 μg/L, $P = 0.000$; 12.03 ± 7.27 versus 4.47 ± 2.48, $P = 0.000$, respectively). Meanwhile, we found that PET/SUV was more than 10 and/or SF was exceed 1000 μg/L usually occurred in patients with LAHS, which might indicated that PET/CT SUVmax and SF level could be used as potential diagnostic factors of LAHS (AUC 0.819 and AUC 0.950, respectively). In our study, Overall survival (OS) of patients with LAHS was inferior to non-LAHS patients (24.3% versus 53.3%). Furthermore, patients with the advanced disease delayed chemotherapy and the survival was discouraging. In addition, PET/CT SUVmax value and SF level were also associated with poor prognosis. Conclusion: Patients with LAHS had poorer outcome than non-LAHS patients. PET/CT and SF level can be used to make early diagnosis of LAHS, and offer prognostic significance for the patients with secondary HLH.

Keywords: Hemophagocytic syndrome (HLH), lymphoma-associated hemophagocytic syndrome (LAHS), prognosis, diagnosis, F-18 FDG PET/CT

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder characterized by immune dysregulation, overwhelming immune activation, and severe inflammation [1]. Prolonged fever, hepatosplenomegaly and pancytopenia are the cardinal symptoms of HLH. And increased ferritin, triglycerides, transaminases, lactate dehydrogenase, soluble interleukin-2 receptor α-chain and decreased fibrinogen are the characteristic laboratory parameters [2]. Etiologies of HLH vary and are different in pediatric and adult patients. HLH is categorized as primary HLH [3] and secondary HLH, which occurs in infections or rheumatological disorders or malignancy [4]. In children, secondary HLH is commonly caused by viral infection. But in adults, hematological malignancies, especially lymphoma, are the main cause of this disease [5].

Lymphoma-associated hemophagocytic lymphohistiocytosis (LAHS), accounting for about 40% of adult secondary HLH, has a higher mortality, and most cases are associated with non-Hodgkin's lymphoma (NHL) [6]. Once the diagnosis of LAHS is confirmed, treatment of lymphoma is important [7]. Therefore, accurate early diagnosis of LAHS is critical to each patient for the purpose of achieving most optimal survival. However, it is difficult because the early clinical manifestations of LAHS are usually atypical [8], and few studies have examined the clinical features and prognostic factors of LAHS in Chinese patients. The aim

Table 1. Etiologies distribution in 67 patients with HLH

Etiologies	Number
Lymphoma-associated HLH	37 (55.22%)
T cell lymphoma	15
B cell lymphoma	10
NK/T lymphoma	8
Aggressive NK cell leukemia	4
Infection-associated HLH	12 (17.91%)
EBV	11
Klebsiella pneumoniae	1
Autoimmune disorders-associated HLH	8 (11.94%)
Systemic lupus erythematosus	2
Undifferentiated connective tissue disease	2
Adult Still's disease	1
Necrotizing lymphadenitis	1
Multiple sclerosis	1
Dermatomyositis	1
Drug hypersensitivity syndrome associated HLH	1 (1.49%)
Unexplained causes	9 (13.43%)

of our study was to investigate the clinical and laboratory features that could distinguish LAHS from non-LAHS patients, and to clarify the prognostic factors of HLH.

Materials and methods

Patients

Between September 2006 and June 2014, 67 adult patients were diagnosed with HLH in our institution. Among them, 37 patients were diagnosed as LAHS. Medical records of all patients in hospital were reviewed. All patients provided informed consents according to the approval of the ethical committee. Diagnosis of HLH was according to the International Histiocyte Society HLH-2004 diagnostic criteria: 1. fever; 2. splenomegaly; 3. cytopenia affecting two or three lineages (hemoglobin < 90 g/L, platelet count < 100×10^9/L, neutrophils < 1.0×10^9/L); 4. hypertriglyceridemia (≥ 3.0 mmol/L) and/or hypofibrinogenemia (≤ 1.5 g/L); 5. hemophagocytosis in bone marrow or spleen or lymph nodes; 6. hyperferritinemia (≥ 500 μg/L); 7. low or absent NK cell activity; 8. soluble CD25 ≥ 2400 U/ml [1]. Due to suitable test methods were unavailable in our institution, NK cell activity and the level of soluble CD25 were not tested in our patients. Diagnosis of lymphoma was confirmed by pathologists according to the WHO 2008 "classification of hematopoietic and lymphoid tissues" [9]. Patients with lymphoma and fulfilled five of the first six criteria of HLH were diagnosed as LAHS.

Laboratory findings and histopathological assessment

All patients underwent physical examinations, hematological tests including complete blood count, liver and kidney function tests, triacylglyceride (TG), lactate dehydrogenase (LDH), β2-microglobulin (β2-MG) and SF assays, coagulation function, and virology and bacteriology tests. Biopsy specimens from involved sites were assessed, as well as bone marrow smears and biopsies. Immunohistochemistry was performed on cell suspensions or paraffin-embedded tissue sections using monoclonal antibodies.

PET/CT scan and image analysis

All patients underwent 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (F-18 FDG PET/CT) scans using a PET/CT scanner system (Discovery ST, GE Healthcare). Patients fasted for at least 6 hours before the intravenous administration of F-18 FDG (7.4 MBq/kg) to ensure a serum glucose level below 7.2 mmol/L. Transmission data was acquired at 60 minutes after the F-18 FDG injection, using the low dose CT (120 kV, automated from 10 to 130 mA, 3.75 mm slice thickness) from the skull base to the upper thigh. PET data were acquired in the same anatomic locations with a 15.7-cm axial field of view in the 3D mode immediately after CT acquisition. The standardized uptake value (SUV) was calculated by dividing the activity measured in each voxel by the total injected activity. All F-18 FDG PET/CT images were read by two experienced nuclear medicine physicians who had no knowledge of clinical information.

Treatment regimens and response

All 67 HLH patients received the treatment according to HLH-2004 treatment protocols [10] including glucocorticoid, etoposide and cyclosporine. Among them, some cases were given high-dose immunoglobulin. Apart from

Table 2. Clinical features in LAHS and non-LAHS groups

	Total (n = 67)	LAHS group (n = 37)	Non-LAHS group (n = 30)	*P* value
Gender				
Male	31 (46.27%)	16 (43.24%)	15 (50.00%)	0.580
Female	36 (53.73%)	21 (56.76%)	15 (50.00%)	
Age (years), mean ± SE	44.43 ± 15.52	48.49 ± 14.48	39.43 ± 15.80	0.017
Fever (≥ 38.5°C)				
Remittent	28 (41.79%)	21 (56.76%)	7 (23.33%)	0.012
Other types	39 (58.21%)	16 (43.24%)	23 (76.67%)	
Effect of antipyretic drugs				
Valid	23 (34.33%)	7 (18.92%)	16 (53.33%)	0.007
Invalid	44 (65.67%)	30 (81.08%)	14 (46.67%)	
Splenomegaly				
Yes	63 (94.03%)	36 (97.30%)	27 (90.00%)	0.318
No	4 (5.97%)	1 (2.70%)	3 (10.00%)	
Hepatomegaly				
Yes	26 (38.81%)	17 (45.95%)	9 (30.00%)	0.183
No	41 (61.19%)	20 (54.05%)	21 (70.00%)	
Lymphonodomegaly				
Yes	35 (52.24%)	23 (62.16%)	12 (40.00%)	0.071
No	32 (47.76%)	14 (37.84%)	18 (60.00%)	
Weightloss				
Yes	31 (46.27%)	23 (62.16%)	8 (26.67%)	0.008
No	36 (53.73%)	14 (37.84%)	22 (73.33%)	

the therapy of HLH, patients with LAHS patients were also treated with chemotherapy. The chemotherapeutic regimens included CHOPE-like (cyclophosphamide, adriamycin, vincristine, glucocorticoid combined with etoposide) or DICE (cisplatin, ifosfamide, etoposide and glucocorticoid). No patients in our study received L-asparaginase or hematopoietic stem cell transplantation (HSCT) treatment.

Treatment response was judged according to the criterias of Cheson et al. [11], and was categorized as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD).

Evaluation of the prognosis of LAHS

When assessing the prognosis of LAHS, it is difficult to clearly differentiate whether the patients died of HLH, progression of original disease, or therapy-related toxicity. Therefore, we decided to analyze prognostic factors for LAHS using the concept of "early death after developing LAHS", which was defined as death within the first 30 weeks after diagnosis of LAHS.

Statistical analysis

Data were expressed as counts and percentages for categorical variables, and mean and SD or median and interquartile ranges or range for normal or skewed quantitative data, respectively. Categorical variables were analyzed using χ^2 or Fisher's exact tests. The Kruskal-Wallis test, Bonferroni test, Mann-Whitney unpaired test and Student's *t*-test were used to determine intergroup quantitative differences. To evaluate the diagnostic values of the examined markers for the differentiation of LAHS, receiver operating characteristic (ROC) curves was constructed and the area under the curve (AUC) was calculated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR^+) and negative likelihood ratio (LR^-) were calculated to explore the best cut-off value for diagnosing LAHS. Overall survival (OS) was defined as the time from initial diagnosis to the time of death or to the time of the first 30 weeks after diagnosis of LAHS. The prognostic significance of the LAHS group, PET/CT SUVmax, age and SF level was assessed by the Kaplan-Meier

Table 3. Laboratory findings in LAHS and non-LAHS groups

	LAHS group (n = 37)	Non-LAHS group (n = 30)	*P* value
Laboratory data, median (interquartile range)			
WBC (× 10^9/L)	1.03 (0.63-3.69)	2.08 (1.07-4.38)	0.145
HGB (g/L)	64.00 (59.00-69.00)	77.00 (68.00-94.00)	0.014
PLT (× 10^9/L)	16.00 (9.00-36.00)	25.00 (12.00-51.00)	0.267
ALT (U/L)	119.00 (67.00-247.00)	140.00 (99.00-419.00)	0.217
AST (U/L)	103.00 (78.00-224.00)	123.00 (50.00-305.00)	0.980
GGT (U/L)	189.00 (60.00-394.00)	224.00 (60.00-358.00)	0.354
ALB (g/L)	25.00 (23.00-28.00)	25.00 (23.00-30.00)	0.718
TBIL (μmol/L)	28.90 (16.10-60.60)	22.10 (12.70-117.90)	0.840
DBIL (μmol/L)	10.70 (6.70-46.10)	10.50 (5.70-81.50)	0.714
LDH (U/L)	844.00 (479.00-1574.00)	568.00 (354.00-840.00)	0.342
β2-MG (mg/L)	5.96 (4.11-7.67)	4.30 (2.82-5.80)	0.091
APTT (s)	36.00 (30.00-51.00)	41.00 (27.00-48.00)	0.830
PT (s)	13.00 (12.00-17.00)	13.00 (11.00-14.00)	0.476
FIB (g/L)	1.20 (0.70-2.40)	1.10 (0.60-1.40)	0.229
TG (mmol/L)	3.44 (3.00-4.87)	3.00 (2.38-4.86)	0.419
Ferritin (μg/L), median (range)	2000.00 (626.00-61800.00)	632.00 (500.00-17000.00)	0.000
PET/CT SUVmax, mean ± SD	12.03 ± 7.27	4.47 ± 2.48	0.000

Note: WBC white blood cell, HGB hemoglobin, PLT platelet count, ALT alanine aminotransferase, AST aspartate aminotransferase, FIB fibrinogen, GGT gamma-glutamyl transferase, ALB albumin, TBIL total bilirubin, DBIL direct bilirubin, LDH lactate dehydrogenase, TG triglyceride, β2-MG β2-microglobulin, APTT activated partial thromboplastin time, PT prothrombin time.

method. Significances of survival were calculated by the log-rank test. Univariate Cox regression analysis was applied to evaluate the influence of factors on OS. Hazard ratios (HR) were calculated to quantify the prognostic effects. All statistical tests were two-sided. Statistical significance was set at $P < 0.05$. All data analyses were performed using the SPSS version 16.0 software.

Results

Etiology distribution in patients with HLH

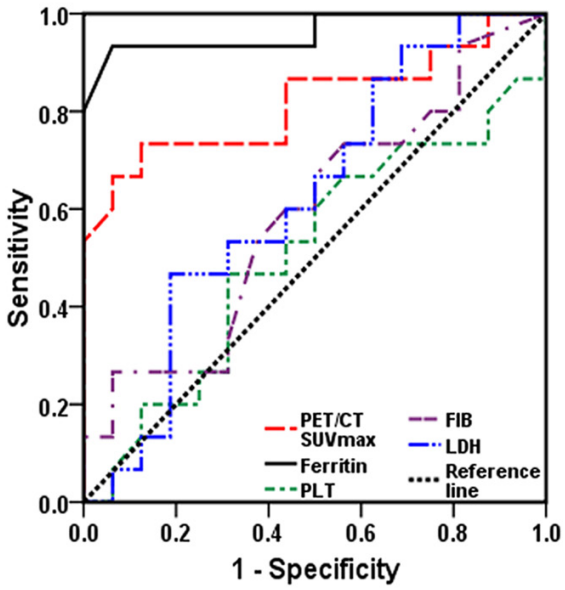
Sixty-seven patients fulfilled the definition of HLH described above. The etiology distribution of these patients is listed in **Table 1**. Among the 67 patients, 37 (55.22%) were LAHS, while 30 (44.78%) were diagnosed as non-LAHS, including EBV infection, autoimmune disorders, drug hypersensitivity syndrome and unexplained causes.

Among the 37 LAHS patients, 22 (59.46%) were diagnosed by bone marrow puncture or biopsy, and 15 (40.54%) were diagnosed by lymph node biopsy. The lymphoma was associated with T cell lymphomas (15 cases, 40.54%) such as peripheral T cell lymphoma, not otherwise specified (PTCL-NOS), subcutaneous panniculitis-like T cell lymphoma (SCPTCL) and anaplastic large cell lymphoma (ALCL). There were NK/T lymphoma and aggressive NK cell leukemia in 12 (32.43%) cases and B cell lymphoma in 10 cases (27.03%).

Clinical and laboratory features of LAHS patients

The clinical characteristics of the patients are summarized in **Table 2**. The mean age was 48.49 ± 14.48 years in the LAHS group and 39.43 ± 15.80 years in the non-LAHS group. Fever occurred in all patients with temperature fluctuating from 38.5°C to 41.8°C. As compared to non-LAHS patients (7/30, 23.33%), more LAHS patients (21/37, 56.76%) had remittent fever ($P = 0.012$) and poorer response to antipyretic drugs (30/37, 81.08% vs. 14/30, 46.67%, $P = 0.007$). In addition, more patients in the LAHS group (23/37, 62.16%) presented weight loss over 10% within six months than those in the non-LAHS group (8/30, 26.67%, $P = 0.008$).

The laboratory findings of the two groups are shown in **Table 3**. In accordance with previous reports [12, 13], the serum ferritin (SF) level of patients in the LAHS group was significantly higher than those in the non-LAHS group ($P =$



	AUC	*P* Value	95% Confidence Interval
Ferritin (μg/L)	0.950	0.000	0.885-1.000
PET/CT SUVmax	0.819	0.002	0.659-0.978
FIB (g/L)	0.590	0.395	0.386-0.793
LDH (U/L)	0.621	0.252	0.420-0.822
PLT ($\times 10^9$/L)	0.508	0.937	0.299-0.718

FIB fibrinogen, *LDH* lactate dehydrogenase, *PLT* platelet

Figure 1. ROC curve analysis of PET/CT SUVmax, serum ferritin level, PLT, FIB and LDH for discriminating LAHS patients from non-LAHS patients, AUC area under the curve.

0.000). As measured in hypermetabolic lesions, the mean value of PET/CT SUVmax in LAHS patients was 12.03 ± 7.27, which was significantly higher than that in non-LAHS patients (4.47 ± 2.48, *P* = 0.000). No significant differences were observed in cytopenia, LDH, β2-MG, aspartate aminotransferase (AST), albumin (ALB), total and direct bilirubin (TBIL and DBIL), fibrinogen (FIB) and TG.

Diagnostic performance of PET/CT SUVmax and ferritin for detection of LAHS

Laboratory data in our study showed that patients with LAHS had higher PET/CT SUVmax value and SF level. The diagnostic performance of the two criteria in differentiating LAHS patients from HLH patients was further evaluated.

Using ROC analysis, the AUC for PET/CT SUVmax in hypermetabolic lesions was 0.819 (95% CI: 0.659 to 0.978) and for SF was 0.950 (95% CI: 0.885 to 1.000), respectively (**Figure 1**). At the cut-off value of 10, the sensitivity and specificity for PET/CT SUVmax was 62.5% and 94.4%, respectively. The cut-off of PET/CT SUVmax was predictive of disease with relatively high PPV of 90.9% and NPV of 73.9%. For SF, at the cut-off value of 1000 μg/L, the sensitivity and specificity was 75.7% and 96.7%, and PPV and NPV was 96.9% and 76.3%, respectively (**Table 4**). This indicated that the optimal cut-off values of PET/CT SUVmax and ferritin could be used as potential diagnostic markers for differentiating between LAHS and non-LAHS patients.

Survival analysis and prognostic factors

All patients in our study (N = 67) were eligible for the survival analysis. With the follow-up of 30 weeks, the OS was 37.3% and the median survival was 6 weeks (range = 1-30 weeks).

Statistically significant differences in the OS rates were observed between the LAHS and non-LAHS patients (24.3% vs. 53.3%, log-rank *P* = 0.008). In LAHS group, five patients diagnosed B cell lymphoma received CHOPE chemotherapy and acquired CR after 3 cycles of chemotherapy. The patients have all survived over 30 weeks. One patient diagnosed SCPTCL receiving DICE chemotherapy has also acquired CR and survived over 30 weeks. Two patients diagnosed PTCL-NOS acquired PR after receiving CHOPE chemotherapy, but had PD soon and survived within 16 weeks. One patient of ALCL only survived for 8 weeks even though acquired SD after CHOPE chemotherapy and died of serious infection. Two NK/T lymphoma patients died in 3 weeks and 6 weeks separately due to hemorrhage and sepsis. The patients were treated with CHOPE chemotherapy at least over 2 weeks after diagnosed HLH. The advanced disease may attribute to delayed chemotherapy. Other patients in LAHS group just received

Table 4. The diagnostic test evaluation indexes of PET/CT SUVmax and serum ferritin in detecting LAHS patients

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR^+	LR^-
Ferritin (μg/L)	> 1000	75.700	96.700	96.600	76.300	22.700	0.252
PET/CT SUVmax	> 10	62.500	94.400	90.900	73.900	11.300	0.397

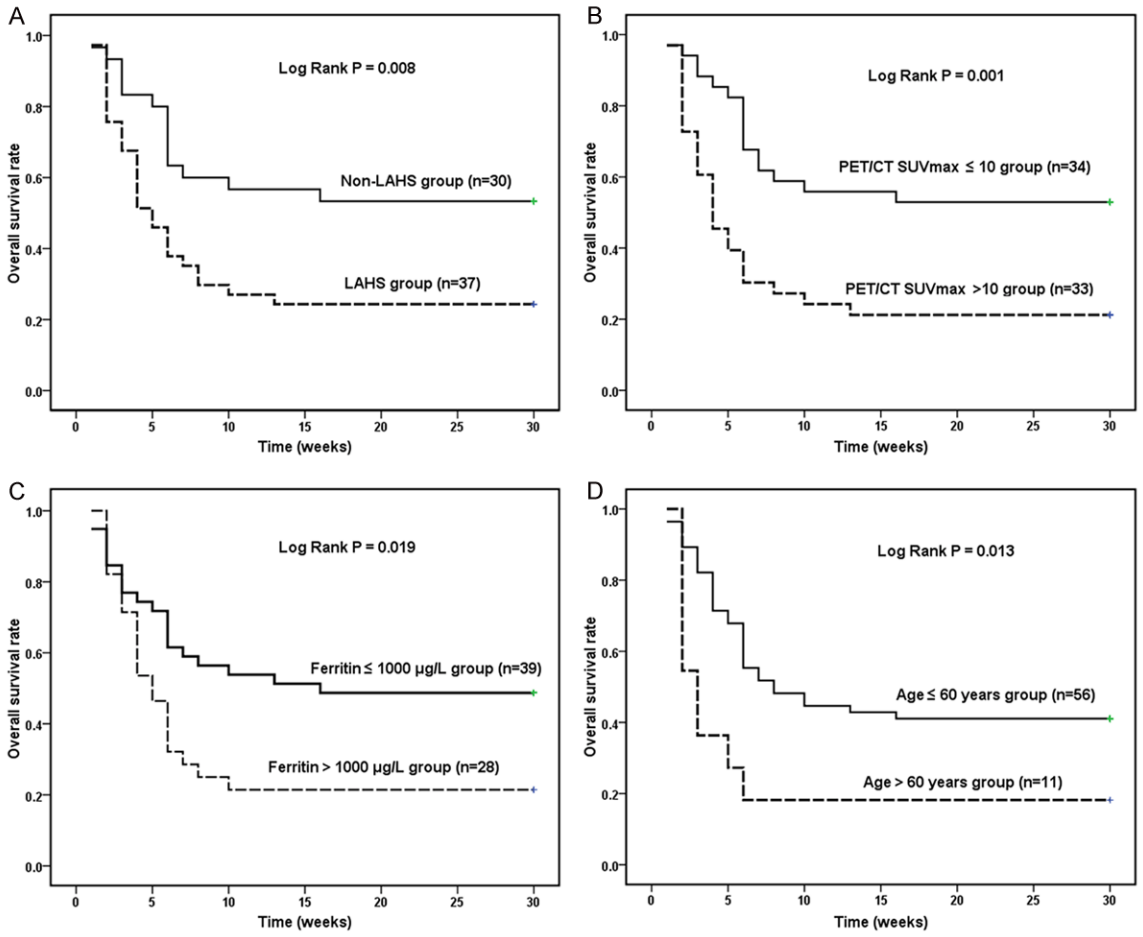


Figure 2. Kaplan-Meier overall survival of patients with LAHS (A), PET/CT SUVmax > 10 (B), serum ferritin level > 1000 μg/L (C) and age > 60 years (D).

HLH-2004 treatment protocols similar to those in non-LAHS group and the median survival time was only five weeks. Accordingly, the overall prognosis of patients in LAHS group was poor.

In addition, patients with PET/CT SUVmax > 10 (21.2% vs. 52.9%, log-rank P = 0.001) or SF level > 1000 μg/L (21.4% vs. 48.7%, log-rank P = 0.019) showed significantly low OS rate. Patients above 60 years also had poor clinical outcome (18.2% vs. 41.1%, log-rank P = 0.013) by Kaplan-Meier analysis (**Figure 2**).

Furthermore, univariate Cox regression analysis was used to assess associations between survival and potential risk factors, including LAHS, age, SF level and PET/CT SUVmax. Except for age, LAHS (P = 0.014, HR = 2.257, 95% CI = 1.183 to 4.307), ferritin level (P = 0.002, HR = 2.527, 95% CI = 1.395 to 4.578) and PET/CT SUVmax (P = 0.002, HR = 1.072, 95% CI = 1.026 to 1.120) were negative prognostic factors (**Table 5**). From the diagnostic value of PET/CT SUVmax and ferritin in discriminating LAHS, their prognostic values may be associated with the poor outcome of LAHS patients.

Table 5. Univariate Cox regression analysis of prognostic factors affecting survival

Factors	HR	95% Confidence Interval	*P* value
LAHS	2.257	1.183-4.307	0.014
Age	1.006	0.986-1.027	0.550
Ferritin level (log_{10})	2.527	1.395-4.578	0.002
PET/CT SUVmax value	1.072	1.026-1.120	0.002

However, Cox multivariate analysis could not be conducted due to the limited sample size.

Discussion

LAHS is known as the major type of secondary HLH in adults [14]. Most cases of LAHS are associated with T cell or NK cell lymphoma [15, 16]. Yu et al. [17] have analyzed 30 patients with lymphoma-associated HLH and found 17 patients (56.7%) had T or NK cell leukemia and 13 (43.3%) patients had B cell lymphoma. Consistent with this previous studies, most LAHS patients (27/37, 73.0%) in our study had T or NK/T cell lymphoma comprising PTCL-NOS, SCPTCL, ALCL, NK/T cell lymphoma and aggressive NK cell leukemia. In contrast, only ten patients (10/37, 27.0%) had B cell lymphoma.

In terms of clinical characteristics, the first manifestation of patients with HLH is prolonged fever of unknown origin. Typical type of fever in the patients with LAHS in our study was remittent fever, which was unresponsive to antipyretic drugs. Besides, consumption symptom such as weight loss was more common in the LAHS group than in the non-LAHS group.

In a study by Han AR et al. [18], patients with LAHS showed a worse prognosis, which was consistent with our results. With the follow-up of 30 weeks, the OS rate of patients with LAHS was lower than those with non-LAHS (log-rank $P = 0.008$). Meanwhile, univariate Cox regression analysis also revealed that early death was related to LAHS ($P = 0.014$, HR = 2.257).

The diagnosis of LAHS depends on the pathological evidence of hematological malignancies in addition to HLH-2004 diagnostic criteria [1]. However, for some patients, it is difficult to find malignant cells via biopsy procedure of involved tissues such as liver, spleen, skin, or lymph nodes and assessment of bone marrow involvement, especially early in the disease course. Moreover, the symptoms of LAHS can be easily confused with non-LAHS, which leads to misdiagnosis. Thus, it is important to explore new methods that can be applied in clinical practice for early diagnosis of LAHS. The F-18 FDG PET/CT, a non-invasive whole-body metabolic imaging technique, is highly recommended for assessment of lymphoma for both improved staging and therapeutic response [19]. The intensity of the FDG uptake is the result of the metabolic activity of the different components of the lymphoma including neoplastic cells and environmental cells. This metabolic activity is usually expressed as SUVmax, which represents the SUV of the point (strictly voxel) with the highest tumor uptake for a given patient. Previous study reported a SUVmax > 10 has been shown as the best cut-off to discriminate aggressive lymphoma from other lesions with 81% specificity [20]. Although SUVmax is a useful indicator for evaluating aggressive lymphoma, only few reports have described the contribution of F-18 FDG PET/CT to the diagnosis of malignancy in patients with HLH [21, 22]. Recently, several studies revealed that F-18 FDG PET/CT might be useful in detecting an underlying malignancy in patients with secondary HLH [13, 23], but the information on the optimal cut-off of SUVmax to differentiate secondary HLH is lacking. In our study, we identified LAHS by biopsy of involved tissues or bone marrow examinations as a gold standard, and found that PET/CT SUVmax was a potential marker for discriminating LAHS patients from non-LAHS cases with an AUC of 0.819. At a cut-off value of 10, the sensitivity was 62.5% and the specificity was 94.4%. Although Yang et al. [24] reported that increased FDG uptake of bone marrow may reflect the level of cytokine storm or the inflammatory status in LAHS, the highest FDG uptake in our study was measured in multiple lymph nodes, spleen or focal hypermetabolic lesions besides bone marrow, which could mimic lymphomatous involvement. Even though inflammatory cells, such as neutrophils and macrophages express high concentrations of glucose transporters [25, 26], we found that as compared to patients with infectious and inflammatory diseases, the PET/CT SUVmax of patients with malignancy was obviously higher (12.03 ± 7.27 vs. 4.47 ± 2.48, $P = 0.000$). Moreover, patients with SUVmax > 10 had an unfavorable prognosis and shorter survival (log-rank $P = 0.001$). Univariate Cox re-

gression analysis showed that PET/CT SUVmax retained poor impact for worse OS (P = 0.002, HR = 1.072). The high group of SUVmax may be associated with the diagnosis of LAHS, which resulted in early death.

In addition to PET/CT SUVmax, other clinical features and laboratory findings of patients with LAHS were also compared with non-LAHS patients. In our study, SF levels were significantly higher in patients with LAHS than in non-LAHS patients. Ferritin is an iron storage protein, whose synthesis is mainly regulated by intracellular iron and inflammatory cytokines [27]. Since ferritin is secreted by activated macrophages and its level is influenced by pro-inflammatory cytokines, it is regarded as an acute-phase reactant protein [28, 29]. A level > 500 μg/L is supportive of HLH [1], however, in our study, the median level of SF in LAHS group was 2000 μg/L which is consistent with the level of B- or T/NK-LAHS reported in some studies [12, 30, 31], higher than those in non-LAHS group. Furthermore, a value > 1000 μg/L has been indicated to be highly specific and diagnostic of LAHS with an AUC of 0.950 in our study. This result is consistent with some recent reports, and may be associated with inflam_mation caused by the lymphoma [12, 30]. Since a high ferritin level is thought to be a nonspecific response of the reticuloendothelial system [32], the specificity of SF may be more valuable which means the patients with SF level lower than 1000 μg/L may be more inclined to non-LAHS. SF is also reported as an important prognostic factor associated with a short survival time in patients with non-Hodgkin's lymphoma [33]. In our study, hyperferritinemia was identified as a poor prognostic factor (P = 0.002, HR = 2.527) and associated with worse survival in patients with HLH (log-rank P = 0.019).

In conclusion, more patients with LAHS showed NK/T or T cell lymphoma and had poorer prognosis. Although most symptoms of LAHS and non-LAHS patients were similar, more patients with LAHS had remittent fever that was unresponsive to antipyretic drugs. In addition, consumption symptoms were more obvious in LAHS patients. Since it is essential but difficult to diagnose LAHS early, we evaluated the significance of F-18 FDG PET/CT and some laboratory indicators in patients with HLH. Our data suggested that PET/CT SUVmax and SF level could distinguish LAHS patients from non-LAHS patients, and may be used as prognostic factors in patients with HLH. Traditionally, pathological biopsy remains the gold standard for diagnosing lymphoma with HLH, if PET/CT SUVmax in focal hypermetabolic lesions exceeds 10, and repeated biopsies of multiple bone marrows from different locations or lymph nodes or hypermetabolic lesions should be actively performed to improve the diagnosis. There are some limitations to this study. Due to the limited number of patients, PET/CT SUVmax combined with SF level for diagnosis of LAHS and multivariate Cox regression analysis was not observed in this study. Further studies with larger sample sizes and multi-center prospective data will help to better understand the detailed pathogenesis of LAHS and improve the prognosis of these patients.

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Disclosure of conflict of interest

None.

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