

# Characteristics and management of patients with hemophagocytic lymphohistiocytosis masquerading as liver failure

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## Research Article

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# Abstract

Liver failure (LF) is a lethal condition characterized by jaundice, coagulation disorders. patients with LF carry a high mortality. Hemophagocytic lymphohistiocytosis (HLH) is established as a rare cause of LF. However, the clinical course of HLH may not be familiar to most hepatologist. We aimed to decipher the characteristics of these patients, to provide experience in the diagnose and management of patients with HLH masquerading as LF. Nine patients initially diagnosed with LF and finally developed HLH between January 2017 and October 2020 were retrospectively included. 78% cases developed LF with no discernable causes. Unexplained cytopenia and recurrent fever with LF may be a red flag for suspicion of HLH. Besides, female maybe predispositional to HLH in the context of LF. Modified DEP regimen was effective to control the fatal inflammatory state, all 9 cases achieved response after only one course. Further, three courses of treatment could substantially make the blood count and liver function return to normalcy, and without recurrence of HLH.

## Introduction

Liver failure (LF) is heterogeneous in etiology and prognosis, it is a life-threatening syndrome, in which rapid deterioration of liver function results in deep jaundice, altered mentation and coagulopathy [1]. The most prominent causes include hepatotoxic drug, viral infection, immune-mediated attack, and hypoperfusion, about one-third of patient even has no discernible cause [1-3]. Albeit rare, a well-established etiology for LF is hemophagocytic lymphohistiocytosis (HLH), thus, a patient may masquerade as LF in the clinical course of HLH [4-6]. Patients may be admitted in a center of hepatology or an intensive care unit for the complaining of deep jaundice and fatigue. Unfortunately, HLH may not be familiar to most physician, therefore, diagnosis of HLH in the context of LF is exceptionally challenging.

HLH has no significant racial or sexual predilection, it is a multisystemic clinicopathologic syndrome characterized by aberrantly activated cytotoxic T cells and macrophages, with resultant hyperinflammation and hypercytokinemia [7]. Clinically, prolonged fever, splenomegaly, cytopenias, hyperferritinemia and hemophagocytosis evidence are the prominent signs of HLH. Although not included in the accepted HLH-04 diagnostic criteria, evidence of liver dysfunction can be found in over 80% patients, ranging from slight elevation of transaminases to LF, thus, LF can be a manifestation of HLH at a certain stage of its development [8-9]. Traditionally, HLH is classified into primary and secondary forms, LF can be the prominent sign of both forms. Underlying genetic defects play a pivotal role in the onset of primary form, secondary HLH are subclassified as infection, autoimmune, or neoplasia related, some cases are still fulfilled HLH even with unknown cause [9-10]. Currently, standard HLH-94, HLH-04 and the salvage DEP regimen have made a remarkable progress in treatment of HLH [11-12]. However, no unanimous therapy has been reached on the treatment of patients with HLH in the context of LF.

As far as the patient management is concerned, it would be a great challenge for gastroenterologists and hepatologists. The reported data showed that patients with LF and HLH have dismal outcome with liver-protective treatment, plasma exchange, glucocorticoids and gamma globulin [5, 13-14]. Liver transplantation may be considered as a curative treatment for LF, however, some researches revealed that HLH is regarded as a controversial indication for liver transplantation considering the systematic nature and risk of

posttransplant recurrence [13-15]. Even though, very expensive cost would be devoted to the treatment of LF and HLH, the results were disappointing.

Based on the current situation, it is self-evident that an optimal therapy beneficial to manage the disease is in urgently need. Studies on HLH in the context of LF are mostly available as case reports. Herein, we carried out a retrospective study to decipher the clinical and laboratory feature of HLH masquerading as LF, aimed to provide key clues for early diagnosis. We also introduce our experience in managing this fatal disease: LF and HLH.

## **Materials And Methods**

### **Subjects and objectives**

We conducted a retrospective cross-sectional study of patients who were newly diagnosed with LF and HLH at one single institution (Beijing Friendship Hospital, Capital Medical University) between January 2017 and October 2020. Informed consent was obtained from all patients or their guardians, agreed to participate in this study. Appropriate ethical approval was approved by Beijing Friendship Hospital Affiliated Capital Medical University in accordance of the Declaration of Helsinki.

In all, 9 patients were referred as cases with imminent or confirmed LF and were admitted to the hepatic diseases center for treatment. In the early stages of the disease, they were diagnosed with LF but not meet the criteria of HLH. In the clinical course, recurrent fever, cytopenia, and other signs of HLH were gradually appeared, they were finally diagnosed with HLH and presented to our center as a hospital transfer for further management of HLH in the context of LF. Data were retrieved including etiological screening, clinical and laboratory features, medical history, HLH genetic testing, treatment, and outcomes.

### **Diagnosis and definition**

The diagnosis of LF had been made according to the 2018 Chinese guideline criteria for diagnosis and treatment of liver failure [2]. The diagnosis of HLH was established in accordance with the internationally accepted guideline of HLH-2004 [16], and the diagnosis was stringently enforced, meeting five out of eight criteria was a necessity.

The efficacy was evaluated at days 14 after initiated every course of modified DEP regimen. Response to therapy was defined as complete response (CR), partial response (PR), and no response (NR) [12]. CR was defined as normalization of clinical symptoms and laboratory parameters of HLH, including levels of sCD25, ferritin, and triglyceride (TG), fibrinogen, hemoglobin (HGB), white blood cell count (WBC), platelet counts (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and direct bilirubin (DBIL). PR was defined as at least a 50 % improvement in two or more laboratory markers. NR was defined as failing to achieve PR.

### **Treatment of HLH**

Modified DEP regimen was as follows (**Figure1**): liposomal doxorubicin 15-25 mg/m<sup>2</sup> d1; Etoposide 100 mg/m<sup>2</sup> d1, methylprednisolone 1-1.5mg/kg d1-5, 0.3-0.6mg/kg d6-14. This two-week regiment will be repeated for 4 courses continuously. The efficacy was evaluated at days 14 after initiating each modified DEP therapy. After 4 courses, methylprednisolone will be tapered gradually. Ruxolitinib was also added when the full-dose glucocorticoid was intolerable, the dose was 0.3mg /kg/day.

## Statistical analysis

Descriptive data is described by median and range, with minimum and maximum values for continuous variables. Categorical statistics are present as number and percentage (%). For intergroup comparison of data, a Mann-Whitney U test and a Wilcoxon rank-sum test were performed. Paired-sample T test was used to compare the changes between groups where suitable. Difference was considered to be significant if the P value was less than 0.05. All the analyses were conducted using SPSS 21.0 (SPSS, Chicago, IL).

## Results

### Characteristics of the patients with LF

As **table 1** displayed, 9 cases with provisional diagnosis of LF were referred from hepatic diseases hospital. Fever was the first prominent signs of most patients, then progressive jaundice and fatigue appeared, 7 patients were diagnosed with acute LF, and the rest 2 cases were subacute LF. The workup for viral hepatitis (IgM-HAV, HBV-DNA, Anti-HCV and IgM-HEV) was negative. Tests for antinuclear antibody spectrum, extractable nuclear antibody spectrum, and anti-neutrophil cytoplasmic antibodies were negative. Anti-mitochondrial antibody was negative and serum ceruloplasmin level was normal. They were all non-drinkers and had no history of liver disease previously. Possible etiology for LF was drug-induced (2 cases), and 7 cases with no discernable causes. Liver-protective treatment together with plasma exchange and glucocorticoid were the main strategies. However, the effect was unsatisfying, pancytopenia and recurrent fever began to be the most pronounced manifestation. Extensive workup was done to evaluate the situation, and then, the signs of hemophagocytosis and elevated ferritin and hypertriglyceridemia were predisposed to the diagnosis of HLH.

### Features of HLH in the context of LF

The features of patients were depicted in **table 2**. The mean time from prodromal to a certain diagnosis of LF was 49.6 days (range, 6-210 days). The average interval from LF to HLH was 22 days (range, 9-50 days). The average time from the first sign of disease to a certain diagnosis of HLH was 71.6 days (range, 20-230 days). Patients were admitted with a median age of 37 years (range: 15-64 years), including 8 females and 1 male (11%), an obvious gender difference was observed.

The laboratory findings of patients at different stage of the disease (provisional diagnosis of LF vs. HLH) were dramatically changed, complete blood count was deeply declined: WBC ( $7.7\pm 3.4$  vs.  $4.1\pm 4.5$ ,  $P=0.038$ ), HGB ( $119.0\pm 20.1$  vs.  $80.4\pm 21.9$ ,  $P=0.008$ ), PLT ( $158.7\pm 86.9$  vs.  $49.8\pm 28.7$ ,  $P=0.008$ ). However, compared with the LF stage, when patients were finally diagnosed with HLH, liver aminotransferase showed some improvement, the level of ALT and AST were markedly decreased: ALT ( $995.3\pm 430.0$  vs.  $251.9\pm 206.2$ ,

P=0.008), AST (957.8±653.5 vs. 366.9±401.7, P=0.038). Intriguingly, the bilirubin were continuously elevated at the stage of HLH diagnosis: TBIL (315.8±113.1 vs. 414.4±244.6, P=0.214), DBIL (206.5±90.1 vs. 255.4±180.7, P=0.515). This phenomenon indicated that unexplained cytopenia and recurrent fever may be a red flag of suspicion of HLH.

All cases present with persistent high-grade fever, 88.9% encountered splenomegaly and hemophagocytosis. Four cases showed pancytopenia, and 4 cases have bicytopenia. Most cases have elevated ferritin over 500ng/mL (8 in 9 cases, 88.9%), elevated soluble IL-2 receptor (sCD25, > 6400pg/mL) were detected in all cases. Decrease nature killer cell activity occurred in 66.7% patients. Besides, hypofibrinogenemia (<1.5 g/L) accounting for 88.9% cases and hypertriglyceridemia (> 3.0mmol/L) was observed in 7 out of all 9 cases.

### **Etiology of HLH in the context of LF**

All patients were extensively evaluated for persistent febrile illness for dengue, malaria, rickettsia, leptospirosis, human immunodeficiency virus and brucella along with blood and urine cultures, which were inconclusive. Herpes virus DNA (epstein-barr virus, cytomegalovirus, herpes simplex viruses, varicella zoster, human herpesvirus 6, human herpesvirus 7, human herpesvirus 8) were all negative. A full-body CT or F-18 fluoro-2-deoxyglucose positron emission tomography/computed tomography scan for malignant tumors (especially lymphoma) was inconclusive. All cases were in absence of HLH family history, genetic test (PRF1, STX11, and UNC13D) were negative, besides, the related protein (perforin, munc 13–4, granzyme B, CD107a, X-linked inhibitor of apoptosis protein, signaling lymphocytic activation molecule associated protein) were roughly normal. Evidence of infection, autoimmune disease and neoplasms were extensively examined. After extensively workup for HLH, one patient was considered as HLH secondary to adult-onset still's disease, other cases were secondary HLH with unknown causes.

### **Treatment with modified DEP regimen, side effects and complications**

All 9 cases in our cohort present with deep jaundice and recurrent fever, most patients underwent a period of time of glucocorticoid treatment before admission. Once diagnosed, HLH-directed treatment was initiated. In all, 6 patients received 4 courses of modified DEP regimen, 3 patients (P1, P5, and P8) underwent prescribed 4 courses of modified DEP regimen. One patient (P2) received one course of full-dose prescribed therapy, then bradycardia occurred, liposomal doxorubicin was withdrawn from the remaining 3 courses. Two cases (P4 and P9) have lower gastrointestinal bleeding after one cycle, appropriately supportive therapies were given, including platelet or clotting factor infusion. The use of glucocorticoid was contraindicated by bleeding, ruxolitinib was added in the remaining 3 courses. The other 3 cases had not completed the whole treating course: 1 case (P3) underwent 2 treatment, her liver test was nearly recovered, she felt well and had no further treatment, 1 patient (P6) received 2 courses of treatment, and then, she had radiological signs of pulmonary, infection was improved after antibiotic treatment, but she did not continue the therapy for economy causes, the patient died of sepsis. A patient (P7) had severe acute pancreatitis and finally succumbed to a fatal for multiple organ failure after 2 courses.

### **Response rate and changes in evaluation indicators after treatment**

A total of 9 patients were diagnosed with HLH in the context of LF, all patients were responsive to the modified DEP regimen, all of the cases achieved PR after 1 course. Of the 6 cases who received 4 courses of treatment, 5 cases achieved CR (83.3%), one case revealed PR (16.7%). In all, after several courses of modified DEP regimen, overall response rate was 100%, 5 cases (55.6%) achieved CR, and another 4 cases (44.4%) got PR.

The parameters were evaluated at HLH diagnosis and at days 14 after initiating each course of modified DEP regimen. These evaluation indicators were concluded in **table 3**. PLT was the first index in blood count to improve. Biotransformation function of liver (ALT, AST, TBIL, DBIL and TG) was markedly improved once HLH-directed therapy was initiated, the index decreased a lot as compared with baseline of HLH diagnosis after only 1 course, these parameters tended to recover to normal after 3 courses (**Figure 2**). To a certain extent, the disorders of liver synthesis were also restored, with the level of fibrinogen and serum albumin dramatically elevated after 1 or 2 courses ( $P=0.038$  and  $P=0.012$ , respectively). The level of sCD25 was also sharply decreased after one course of therapy.

No case experienced HLH recurrence at a median of 14.8 months (range, 1.35-27.5 months) after treatment. Two patients died (overall survival rate 77.7%), six patients were alive and well at a median of 16 months (range, 5.2-27.5 months).

## Discussion

We reported a single center experience of 9 patients with HLH in the context of LF. HLH has a wide spectrum of clinical manifestations, however, LF as a presentation of HLH is a rare and serious condition with very high mortality and morbidity [4-6]. LF may dominated the clinical presentation in HLH patients at a certain early stage of the disease, patients usually received LF-directed therapy at a department of hepatology [6]. Our study was powered to decipher characteristics and management of this group of patients. The average time from the first sign of disease to a certain diagnosis of HLH was 71.6 days, therefore, awareness of HLH may be the most important to early diagnosis. Besides, according to the reports, women were predispositional to HLH in the context of LF and most cases had indeterminate cause for LF [6, 17]. Our results were similar to the document, in our cohort, an obvious gender difference was observed, with 8 women and 1 man in all patients, thus female maybe predispositional to HLH patients in the context of LF. Besides, most patients with LF were also had no discernable causes. Therefore, in female patients with LF of indeterminate etiology, HLH should be suspected with a high degree, especially at the following conditions: unexplained progressively cytopenia, recurrent fever. A high index of suspicion is an indispensable condition for prompt diagnosis and fatal disease prevention. Additionally, hemophagocytosis in bone marrow and the increased level of sCD25 were indicators for HLH with high sensitivity.

HLH can occur simultaneously with LF, lag behind LF or develop during the treatment [5-6, 18]. In our cohort, diagnosis of HLH lagged behind LF, the average interval from LF to HLH was 22 days. Complete blood count sharply decreased at HLH diagnosis compared to stage of LF, however, amelioration of liver function was also detected, with the level of ALT and AST dropped markedly. According to the report [6], TBIL is also decreased when HLH was diagnosed, however, it is worth noting that patients in our cohort had a tendency for increased bilirubin as with the progressing of LF to HLH. To date, reasons of liver injury in HLH remain

unknown, potential mechanism were: hepatocyte necrosis, activated macrophages and T cell–predominant cellular infiltrate in the portal tracts, interferon-gamma pathway upregulation in the liver tissue and systemic inflammatory or immune-targeted injury [13, 19-20]. All form of HLH can occur LF prior to HLH, the etiology of HLH were mostly inconclusive [4, 13]. Etiology causes of HLH was extensively scrutinized, similar to the documented data, one patient was considered as HLH secondary to adult-onset still's disease, the remaining 8 cases were secondary HLH without conclusive underlying disease.

The in-hospital mortality rate was significantly higher in cases of secondary or primary HLH presenting with LF [6, 21]. At present, there is no unanimously recommended therapy on the management of coexistence of two clinical conditions: LF and HLH. Liver-protective treatment together with plasma exchange and glucocorticoid were the main strategies for LF, when HLH encountered, cyclosporine, intravenous immunoglobulin, etoposide or fludarabine were once attempted, however, about half patients succumbed to progression disease [4-5, 22]. Though, case series studies reported that about 67% patients with LF and HLH stay alive after liver transplantation, however, over half of these alive cases experienced HLH recurrence [13-14]. Thus, liver transplantation may be a potentially lifesaving intervention, but it would not resolve underlying problems. Additionally, considering donor source and huge cost, liver transplantation is difficult to implement for most patients in development countries.

DEP regimen was firstly described as a salvage treatment for relapse or refractory HLH, however, complications such as bleeding, myelosuppression, and infection were also observed [12]. Etoposide electively depleted activated T cells leading to suppression of inflammatory cytokines, thus etoposide was regarded as the core HLH treatment [23]. It was regarded that the use of etoposide may be contraindicated by LF, however, out data showed that dose adjusted DEP regimen, etoposide, doxorubicin and methylprednisolone were well tolerated in the patients with HLH and LF. Response to therapy was evaluated by clinical and laboratory evidence of resolution. All patients achieved PR after just one course of modified DEP regimen, with improved index of biotransformation function and blood count, also with decreased sCD25 and ferritin. Three courses of treatment would enough to restore the function of liver and fully control the HLH. It is intriguing that no case experienced HLH recurrence after treatment. Altogether, modified DEP regimen would be a potentially lifesaving intervention that allows for a cure of HLH in the context of LF.

Despite retrospective nature and limited sample size, our study depicted the clinical and laboratory features of HLH in the context of LF, the indicative information may provide clues for early diagnosis of HLH which masqueraded as LF. In relation to treatment, modified DEP regimen can effectively restore the liver function and cure HLH.

## Abbreviations

LF, liver failure; HLH, hemophagocytic lymphohistiocytosis; CR, complete response; PR, partial response; NR, no response; TG, triglyceride; HGB, hemoglobin; WBC, white blood cell count; PLT, platelet counts; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin

## Declarations

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## Authorship Contributions

Y.Y. contributed to the study design, data analysis and interpretation, and writing the report. J.W. and Z.W. contributed to patient registration and treatment, data collection, and writing and approval of the manuscript. All other authors contributed equally to data collection and review of the manuscript. No medical writer was involved in the study and the manuscript.

## Conflict of interest statement

The authors declared that they have no commercial, proprietary, financial interest or any potential conflicts in the producers or companies described in this manuscript. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Besides, the information has never been presented in any meeting previously.

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**Competing Interests:** The authors declare no competing interests.

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## Tables

Table 1. Characteristics of the patients at the diagnosis of liver failure

Patient	Sex	Age	Type of LF	Etiology	Prodromal to LF	Interval from LF to HLH	Underlying disease	Alcohol intake
1	F	37	ALF	NF	68	24	NF	N
2	M	15	ALF	NF	65	20	NF	N
3	F	64	SALF	Drug	210	27	HT, DM	N
4	F	25	ALF	NF	21	24	NF	N
5	F	40	SALF	NF	47	20	NF	N
6	F	43	ALF	Drug	10	50	Uterine fibroid	N
7	F	15	ALF	NF	14	10	NF	N
8	F	24	ALF	NF	6	14	NF	N
9	F	55	ALF	NF	32	9	NF	N

Abbreviations: F, female; M, male; ALF, acute liver failure; SALF, subacute liver failure; NF, not found; HT, hypertension; DM, diabetes mellitus; N, no

Table 2. Features of hemophagocytic lymphohistiocytosis in the context of liver failure

As at diagnosis	Patients								
	1	2	3	4	5	6	7	8	9
Items fulfilled	7	7	7	7	8	7	8	7	6
Recurrent fever	Y	Y	Y	Y	Y	Y	Y	Y	Y
Splenomegaly	Y	Y	Y	Y	Y	Y	Y	Y	N
Emphagocytosis	N	Y	Y	Y	Y	Y	Y	Y	Y
Leucopenia	N	N	Y	Y	Y	N	Y	N	N
Cytopenia	Y	Y	N	N	N	Y	N	N	Y
Uric acid (ng/mL)	2077	10468	736	144.7	1533.4	825	3379	15000	41223
CK activity (%)	14.57	20.12	17.87	10.05	12.08	16.27	13.74	13.60	16.17
IL-25 (pg/mL)	14219	35017	10168	8140	25817	10186	11389	11934	20714
Urea (mmol/L)	5.51	3.64	1.35	4.5	3.6	2.15	3.01	6.45	3.46
Fibrinogen (g/L)	0.94	0.83	0.99	1.44	0.64	0.78	1.36	1.49	1.95
WBC ( $\times 10^9/L$ )	3.09	2.93	1.65	0.5	1.88	2.76	1.04	9.08	13.95
PLT ( $\times 10^9/L$ )	2.17	1.2	0.7	0.27	0.77	2.51	0.5	7.1	12.43
HGB ( $\times 10^9/L$ )	0.36	1.1	0.42	0.15	1.04	0.51	0.4	0.51	0.75
Albumin (g/L)	56	79	87	74	60	67	75	127	99
β <sub>2</sub> -MG ( $\times 10^9/L$ )	64	17	16	77	42	36	83	88	25
ALT (U/L)	87	617	20	218	168	27	272	474	384
AST (U/L)	96	1111	40	85	53	54	386	789	688
TBIL (umol/L)	199	827	171	739	340	233	602	280	339
DBIL (umol/L)	107	626	101	353	233	140.9	434	181	123
ALP (U/L)	304	166	99	193	153	210	137	142	155
GGT (U/L)	299	55	173	160	275	354	197	506	111
Albumin (g/L)	37.5	33.6	33.1	29.7	29.8	34.0	31.2	27.1	24.3
IL-6 (U/L)	679	1124	240	218	380	249	264	1153	736
β <sub>2</sub> -MG (mg/L)	3.64	6.09	3.5	3.42	3.43	3.02	1.69	7.03	4.42
Thyroidopathy	Y	Y	Y	N	Y	Y	Y	Y	Y
Diabetes	Y	N	N	N	Y	N	Y	Y	N
Thrombocytopenia	Fever	Fever	Jaundice	Fever	Fever	Fever	Fever	Fever	Fever
Log <sub>10</sub>	NA	NA	NA	NA	NA	NA	NA	NA	AOSD

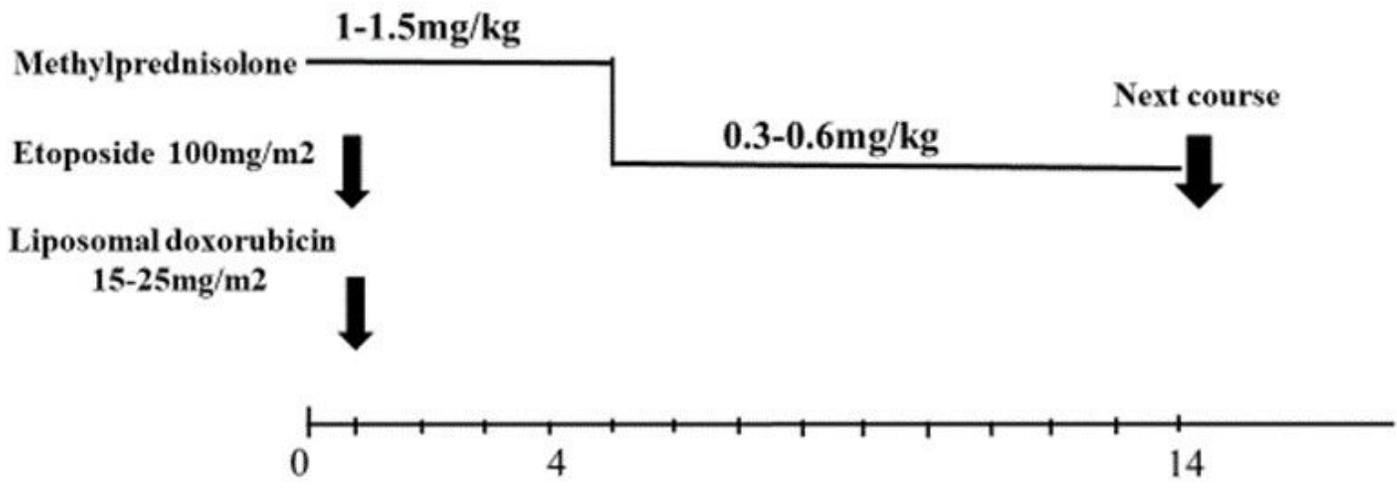
Abbreviations: NK – natural killer; TG, triacylglycerol; WBC, white blood cells; HGB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; LDH, lactic dehydrogenase; MG, macroglobulin. Reference range: WBC:  $3.5-9.5 \times 10^9/L$ , HGB: 130-175 g/L; PLT:  $125-350 \times 10^9/L$ ; ALT: 7-40 u/L; AST, 9-50 u/L (M); AST: 13-35 U/L (F), 15-40 U/L (M); TBIL: 3.4-17.1 umol /L; DBIL: 0-6.8 umol/L; ALP: 45-125U/l γ-GGT: 10-60 U/L; albumin: 40-60g/L; LDH: 120-250U/L; β<sub>2</sub>-MG: 1.09-2.53 mg/L

Table 3. Response rate and changes in evaluation indicators before and after treatment of different course of modified DEP regimen.

	Diagnose-HLH (n=9)	1 course (n=9)	2 courses (n=8)	3 courses (n=6)	4 courses (n=6)
WBC ( $\times 10^9/L$ ) value	4.1 $\pm$ 4.5	6.1 $\pm$ 6.3	6.9 $\pm$ 4.4	5.2 $\pm$ 1.7	9.2 $\pm$ 5.5
HGB (g/L) value	80.4 $\pm$ 21.9	83.7 $\pm$ 13.6	84.8 $\pm$ 18.0	92.8 $\pm$ 16.0	115.8 $\pm$ 14.1
PLT ( $\times 10^9/L$ ) value	49.8 $\pm$ 29.7	157.2 $\pm$ 118.1	181.4 $\pm$ 85.6	152.00 $\pm$ 85.9	197.6 $\pm$ 78.7
ALT (U/L) value	251.9 $\pm$ 206.2	111.1 $\pm$ 106.5	47.6 $\pm$ 46.3	44.2 $\pm$ 24.4	25.8 $\pm$ 11.7
AST (U/L) value	367.0 $\pm$ 401.7	81.3 $\pm$ 74.6	33.5 $\pm$ 27.2	36.9 $\pm$ 11.2	22.8 $\pm$ 8.1
TBIL (umol/L) value	414.4 $\pm$ 244.6	167.4 $\pm$ 134.2	63.3 $\pm$ 47.9	25.2 $\pm$ 16.4	15.2 $\pm$ 13.8
DBIL (umol/L) value	255.4 $\pm$ 180.7	95.3 $\pm$ 92.0	28.7 $\pm$ 25.4	9.8 $\pm$ 8.9	3.3 $\pm$ 3.1
ALP (U/L) value	173.2 $\pm$ 58.6	175.9 $\pm$ 105.6	138.8 $\pm$ 84.9	142.2 $\pm$ 96.3	113.2 $\pm$ 72.9
GGT (U/L) value	236.7 $\pm$ 136.8	200.0 $\pm$ 93.2	204.1 $\pm$ 139.7	176.7 $\pm$ 140.4	79.4 $\pm$ 58.3
TG (g/L) value	31.1 $\pm$ 4.0	31.4 $\pm$ 3.7	40.1 $\pm$ 3.8	37.5 $\pm$ 6.5	37.7 $\pm$ 4.1
LDH (U/L) value	560.3 $\pm$ 379.3	397.0 $\pm$ 210.5	278.1 $\pm$ 85.9	447.1 $\pm$ 268.8	207.8 $\pm$ 43.9
Uricin (ng/mL) value	8736 $\pm$ 13331	3022 $\pm$ 3112	1982 $\pm$ 3898	10780 $\pm$ 22725	1377 $\pm$ 2831
D25 (pg/mL) value	16398 $\pm$ 9010	4272 $\pm$ 3202	2627 $\pm$ 3102	2174 $\pm$ 2176	2211 $\pm$ 2293
Urea (mmol/L) value	3.74 $\pm$ 1.58	2.54 $\pm$ 1.13	1.61 $\pm$ 0.74	1.19 $\pm$ 0.29	1.89 $\pm$ 0.63
Creatinogen (g/L) value	0.98 $\pm$ 0.38	1.27 $\pm$ 0.25	1.70 $\pm$ 0.56	1.74 $\pm$ 0.95	2.85 $\pm$ 0.75
Response rate					
R, n (%)		0	1 (12.5%)	4 (66.7%)	5 (83.3%)
R, n (%)		9 (100%)	7 (87.5%)	2 (33.3%)	1 (16.7%)

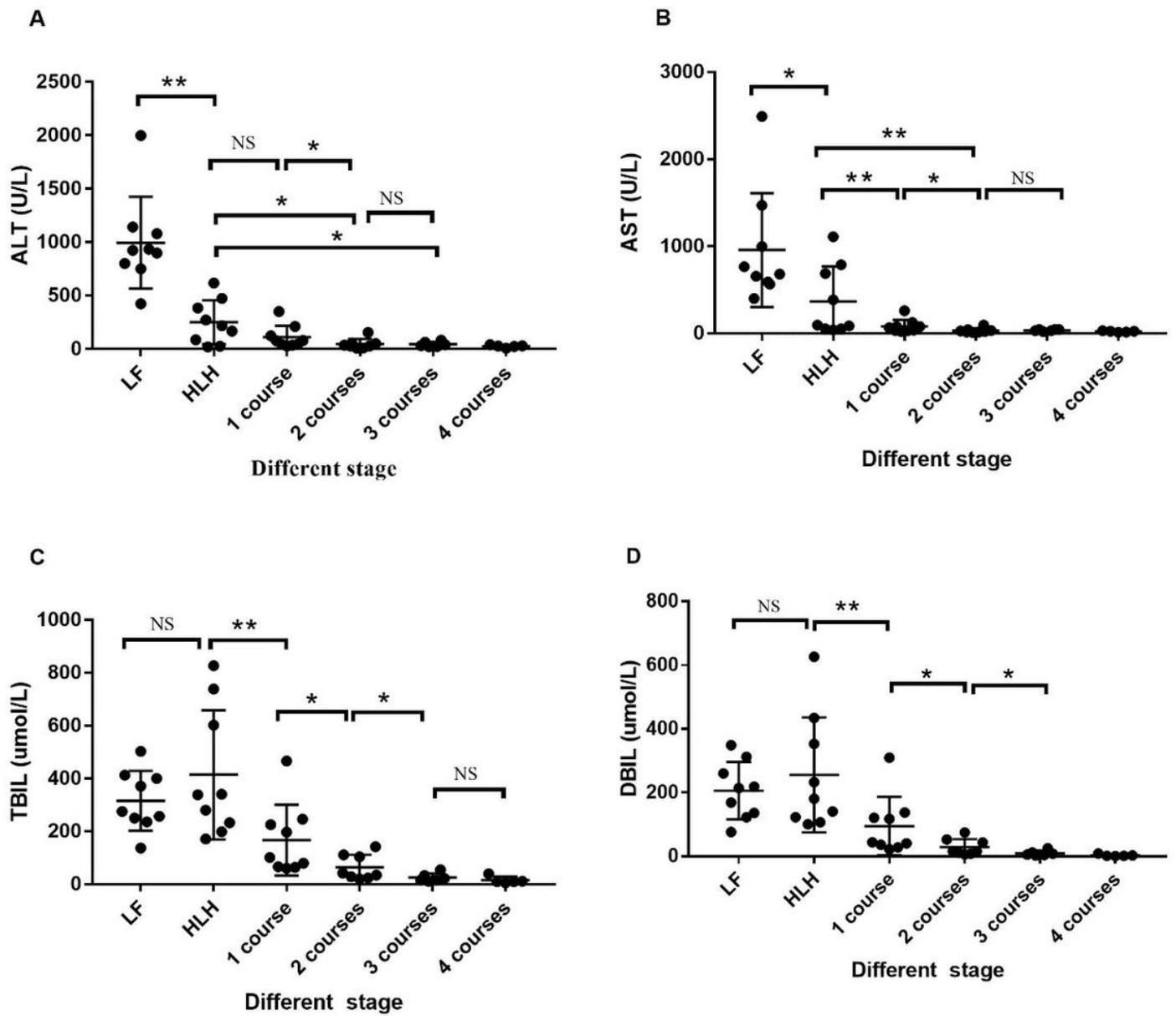
a: HLH vs. 4 courses; b: HLH vs. 1 course; c: HLH vs. 2 courses; d: 1 course vs. 2 courses; e: HLH vs. 4 courses; f: HLH vs. 3 courses; Abbreviations: WBC, white blood cells; HGB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; LDH, lactic dehydrogenase; TG, triacylglycerol.

## Figures



**Figure 1**

Dosage of modified DEP regimen. The horizontal axis of this figure is a timeline, split into days



**Figure 2**

Changes of biotransformation function of liver at different stage of HLH, patients diagnosed with liver failure (LF), hemophagocytic lymphohistiocytosis (HLH) and after different course of modified DEP regimen. \*  $P < 0.05$ , \*\*  $P < 0.01$