Am J Transl Res 2025;17(3):1604-1612
www.ajtr.org /ISSN:1943-8141/AJTR0162515

Review Article

Advances in diagnosis and treatment of lymphoma-associated hemophagocytic syndrome

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Received December 6, 2024; Accepted January 13, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Hemophagocytic syndrome (HPS) is a rare clinical disorder characterized by persistent and ineffective activation of the immune system, leading to a severe systemic inflammatory response. Lymphoma-associated hemophagocytic syndrome (LAHS) refers to HPS caused either by lymphoma itself or by immunosuppression during lymphoma chemotherapy at present, there is no standardized consensus on the diagnosis and treatment of LAHS, both domestically and internationally. After remission induced by combination chemotherapy, hematopoietic stem cell transplantation (HSCT) is a commonly used treatment approach. This paper reviews the latest advancements in the diagnosis and treatment of LAHS, providing a reference for its clinical management.

Keywords: Lymphoma-associated hemophagocytic syndrome, pathogenesis, diagnosis, treatment, prognosis

Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a form of lymphohistiocytosis characterized by the death of natural killer (NK) cells and decreased or absent cytotoxic T lymphocyte (CTL) function. This results in the abnormal proliferation and activation of lymphocytes and macrophages, leading to the excessive release of cytokines and subsequent organ infiltration and tissue damage [1]. Clinical manifestations of HLH are diverse, including fever, hepatosplenomegaly, rash, lymphadenopathy, and neurological symptoms in the early stages. Laboratory findings typically show hemocytopenia, elevated serum ferritin, triglycerides, and sCD25 levels, decreased fibrinogen, reduced NK cell activity, and the presence of hemophagocytosis in bone marrow, spleen, or lymph node biopsies. Common causes of death include bleeding, infection, multiple organ failure, and disseminated intravascular coagulation (DIC) [2]. HLH can be classified into two types based on etiology: familial HLH (fHLH) and secondary HLH (sHLH). Secondary HLH is primarily triggered by infections, tumors, and autoimmune diseases. Among tumor-associated HLH cases, T/NK cell lymphoma accounts for 35.2%, B-cell lymphoma 31.8%, Hodgkin lymphoma 5.8%, leukemia 6.4%, other hematologic tumors 14.4%, solid tumors 3.0%, and unclassified tumors 3.2% [2]. In summary, lymphoma is the most common primary cause of tumor-associated HLH, referred to as lymphoma-associated hemophagocytic syndrome (LAHS).

LAHS is either directly caused by lymphoma or occurs during chemotherapy for lymphoma. Based on the onset time, it is categorized into lymphoma-induced HLH and chemotherapy-induced HLH [3] (**Figure 1**). Diagnosis of LAHS requires meeting both HLH diagnostic criteria and a pathological diagnosis of lymphoma. Appropriate treatment measures should be implemented for confirmed cases. This review aims to summarize current studies on the diagnosis and treatment of LAHS to provide clinical reference.

https://doi.org/10.62347/TVTB3045

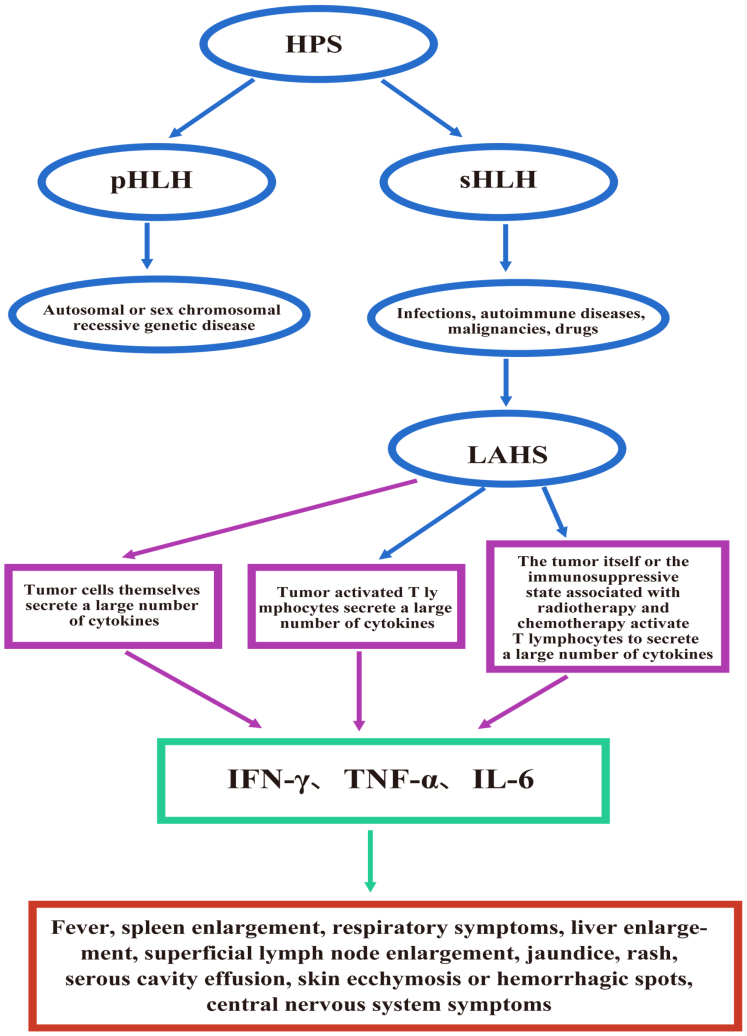

Figure 1. Pathological and physiological processes of lymphoma-associated hemophagocytic syndrome. HPS, Hemophagocytic syndrome; LAHS, Lymphoma-associated hemophagocytic syndrome; pHLH, primary hemophagocytic lymphohistiocytosis; sHLH, secondary HLH.

Pathogenesis of HLH

Immune activation

The exact mechanism of HLH remains unclear but is believed to involve abnormal immune system activation. Studies suggest that granule-mediated cytotoxic defects may be a common mechanism for both familial and secondary HLH [2]. Various factors lead to dysregulated cellular immune responses, which may arise from an imbalance between type 1 helper T cells (Th1) and type 2 helper T cells (Th2) [4]. Th1 cells primarily secrete interleukin (IL)-2, IL-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)-β, mediating cellular immunity. Th2 cells mainly secrete IL-4, IL-5, and IL-9, promoting humoral immunity [5]. Numerous studies have shown that secondary HLH (sHLH) is associated with Th1 polarization [6-8], characterized by excessive activation of the Th1 response, the release of large amounts of cytokines, and subsequent activation of cytotoxic T lymphocytes (CTL) and macrophages, resulting in a "cytokine storm". Impaired NK cell activity is also a key factor in uncontrolled immune responses and is linked to prognosis. A significant reduction in NK cell numbers and an increase in CTL numbers are associated with a poor prognosis. This abnormal immune response leads to the attack of normal tissues and cells, causing tissue damage and progressive multi-organ failure [4] (**Table 1**).

Additionally, Epstein-Barr virus (EBV) infection can chronically activate B lymphocytes and the mononuclear macrophage system, impairing the immune surveillance function of T lymphocytes and leading to immune response disorders, which may also contribute to HLH pathogenesis [9]. Recent studies suggest that gene variations related to HLH could be crucial in determining the severity and treatability of adult HLH [10]. In adults, HLH is commonly associated with tumors, autoimmune diseases, and infections. Certain medications, such as lamotrigine, an antiepileptic drug, can also induce HLH [11, 12]. In the case of LAHS, the pathogenesis is likely linked to neoplastic lymphocyte proliferation and abnormal cytokine secretion. Somatic mutations in the FAS pathway have been reported to increase the risk of HLH in NK/T cell lymphoma [13] (**Figure 2**).

HLH-related gene mutations

Multiple gene mutations are known to be closely associated with HLH. The PRF1 gene, which

Table 1. The abnormal activation of the immune system and HLH

Disruption of the balance between Th1 (Excessive activation) and Th2	Other factors
IL-2, IL-12, IFN-γ and TNF-β (Up-regulation)	NK cell activity was impaired/ Epstein-Barr virus infection
Th1 is over-activated and secretes a large number of cytokines, forming a factor storm	Abnormal immune response attacks/ Immune response disorders

HLH, hemophagocytic lymphohistiocytosis; IL-2, Interleukins-2; IL-12, Interleukins-12; IFN-γ, Interferon-γ; TNF-β, tumor necrosis factor-β; Th1, type 1 helper T cells; Th2, type 2 helper T cells.

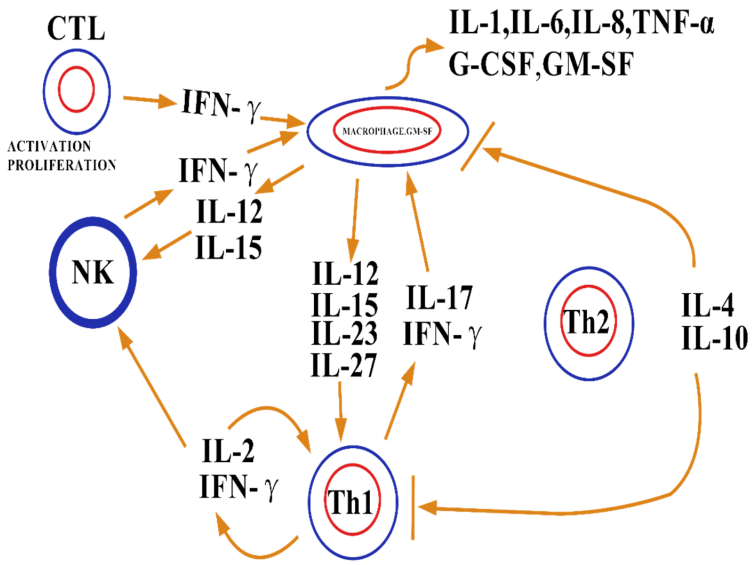

Figure 2. Signal pathway diagram of HLH pathological process. CSF, cerebrospinal fluid; HLH, hemophagocytic lymphohistiocytosis.

encodes perforin, was the first identified familial HLH (FHLH)-related gene. Subsequently, other mutations have been discovered, including UNC13D (encoding MUNC13-4), STX11 (encoding syntaxin 11), and STXBP2, which cause abnormal degranulation of lymphocytes. Additionally, mutations in genes such as RAB27A (in Griscelli syndrome type II), LYST (in congenital leukocyte granule deficiency syndrome), and AP3B1 (in Hermansky-Pudlak syndrome) affect intracellular granule transport, leading to pigmentation defects in cytotoxic T cells, platelets, and neutrophils. Mutations in SH2D1A and BIRC4/XIAP genes in X-linked lymphoproliferative syndrome (XLP1 and XLP2) result in immune dysfunction, making the body more susceptible to EEBV infections and potentially leading to HLH.

Research has shown that PRF1 mutations can induce childhood HLH, with most FHLH patients being exposed to numerous vaccines or infections during the first year of life. However, it remains unclear whether PRF1 deficiency alone can trigger HLH in the absence of other immune or external triggers. HLH patients with concurrent infections may exhibit down-regulated immune function, potentially progressing to immune deficiency. The first established HLH mouse model, with a PRF1 gene deletion, showed that lymphocytic choriomeningitis virus could induce HLH, suggesting that HLH may involve a spectrum of lymphocytic diseases rather than a strict division into primary and secondary forms.

An in vitro study on HLH genotype/phenotype-related cytotoxic functions confirmed a correlation between gene mutations and age, indicating that gene mutations lead to loss of protein function, which manifests as early disease onset. Moreover, mutations in subfunctional genes may contribute to the initial clinical manifestations of adult HLH. A large cohort study revealed that 14% of diagnosed adult HLH cases had gene mutations causing dysfunction or polymorphism, with some cases presenting after the age of 70.

Additionally, certain patients exhibit genetic patterns in HLH-related gene mutations, such as mutations in alleles of two different degranulation-related genes (e.g., Rab27a, UNC13D, STXBP2, STX11), a phenomenon commonly observed in children. This can also present as abnormalities in degranulation genes and single allele deletions of the PRF1 gene, which tends to have a later onset. Further studies have identified that T lymphocyte functional abnormalities, related to IL-2-mediated T cell kinase (ITK), CD27, and magnesium transport

Table 2. HLH and organ injury

Tissue and organ	Injury manifestation
Skin	Rash, edema, ecchymosis or purpura
Liver	A liver biopsy can reveal hepatocyte necrosis and blood phagocytosis
Respiratory system	Cough, dyspnea and respiratory failure
Non-specific gastrointestinal symptoms	Diarrhea, nausea, vomiting, and abdominal pain may also present as gastrointestinal bleeding, pancreatitis, or ulcerative bowel disease
Kidney	Renal failure or nephrotic syndrome
Central nervous system dysfunction	Epilepsy, disorders of consciousness, ataxia, dystonia, meningitis, cavernous sinus syndrome, cerebral hemorrhage, cerebral infarction, etc.

HLH, hemophagocytic lympho histiocytosis.

genes (MAGT1, associated with XMEN), are linked to EBV infection and HLH.

Approximately half of childhood HLH cases are associated with genetic defects, with variation in incidence across regions and ethnicities. It is anticipated that additional HLH-related genes will be discovered in the future.

High inflammatory response

The distinction between high-inflammatory-response HLH and systemic inflammatory response syndrome remains unclear. In HLH, excessive activation of lymphocytes and macrophages leads to the destruction of normal cells, resulting in the release of large quantities of cytokines (IFN-γ, TNF-α, IL-6, MCSF) into the bloodstream. Dysfunction of NK cells and cytotoxic T lymphocytes can be observed in both familial and acquired HLH. In mouse models, the release of IFN-γ by CD8+ T cells is a key factor triggering the HLH phenotype. Studies have shown that the levels of IFN-γ-related proteins in the plasma of HLH patients are significantly higher than those observed in inflammatory responses under other conditions. Under normal circumstances, CD8+ T lymphocytes produce large amounts of cytokines in response to antigen stimulation, with sensitized T cells directly killing antigens, while cytokines enhance this cytotoxic effect. However, when this state persists, T cells undergo uncontrollable excessive activation and proliferation, ultimately leading to the development of HLH.

Clinical features

Non-specific manifestations of organ injury

The initial symptoms of HLH lack specificity, and clinical manifestations are typically acute or subacute (1-4 weeks), with persistent high fever and enlargement of lymph nodes, liver, and spleen being the most common signs [2]. HLH can trigger a systemic inflammatory response affecting various organs. Non-specific skin involvement, such as rash, edema, ecchymosis, or purpura, can also occur. HLH can cause progressive multi-organ failure, and most patients require intensive care. Organ involvement may be due to the patient's underlying disease, infections, or complications associated with HLH itself. The liver and spleen are the most commonly affected organs, with liver biopsy showing liver cell necrosis and blood phagocytosis [14]. HLH often affects the lungs, leading to symptoms such as cough, dyspnea, and respiratory failure [15], most commonly caused by respiratory viral infections. Non-specific gastrointestinal symptoms, including diarrhea, nausea, vomiting, and abdominal pain, may also manifest, with complications such as gastrointestinal bleeding, pancreatitis, or ulcerative bowel disease [16]. Renal involvement often presents as renal failure or nephrotic syndrome, and approximately 50% of patients require hemodialysis (**Table 2**).

Central nervous system (CNS)-HLH

CNS-HLH involvement can be the initial clinical manifestation of HLH or may occur later in the disease course. (1) Symptoms/signs: these may include mental and/or neurological symptoms, such as irritability, altered consciousness, epilepsy, seizures, meningeal irritation, ataxia, and hemiplegia. (2) Imaging abnormalities: head MRI may show brain parenchymal or meningeal abnormalities. (3) Abnormal cerebrospinal fluid (CSF): this may show an increased cell count and/or elevated protein levels in the CSF [17-19]. Some patients may also

experience personality changes, delirium, and other psychiatric symptoms [20]. CNS involvement in HLH often indicates a poor prognosis, and untreated HLH may eventually lead to CNS complications [21]. Therefore, early diagnosis and treatment of HLH are crucial.

Diagnosis

At present, there is no unified diagnostic criteria for LAHS. In 2018, the Lymphoma Professional Committee of the Chinese Anti-Cancer Association proposed diagnostic criteria for LAHS [22], which stipulate that the diagnosis should meet both the pathological diagnosis of lymphoma and 5 of the 8 HLH-2004 diagnostic criteria [23]. In 2022, experts from the Lymphoma Professional Committee of the Chinese Anti-Cancer Association updated the 2018 edition of the Chinese Expert Consensus on the Diagnosis and Treatment of Lymphoma-Associated Hemophagocytic Syndrome, based on evidence from medical literature, both domestic and international. However, the specific diagnostic criteria changed little [3]. Despite efforts by scholars from various countries to propose more targeted diagnostic criteria that are better suited to clinical practice in recent years, no consensus has been reached [24-26]. Both the original and updated diagnostic criteria for LAHS have their strengths and limitations. Some items in the HLH-2004 standard (e.g., soluble CD25, NK cell functional activity) may not be practical in clinical settings, especially when the disease progresses rapidly, laboratory test results take time to return, or the patient's medical and financial conditions are limited. In contrast, the 18 diagnostic criteria proposed by Tamamyan et al. [27] are easier to implement across different levels of hospitals, aiding clinicians in making early diagnoses of HLH. However, including more clinical and laboratory tests could lead to an expanded diagnosis and an increased risk of false positives. Therefore, the diagnostic criteria for LAHS need to be further refined in future studies to enhance their clinical applicability.

Treatment

Treatment for LAHS involves two main aspects. First, induction therapy for HLH is used to control disease progression by inhibiting the inflammatory response and improving organ dysfunction. Second, the primary treatment for lymphoma is aimed at preventing HLH recurrence through etiological treatment. There is currently no evidence-based guidance on whether HLH or lymphoma should be treated first. The main approach involves sequential HSCT therapy following remission induced by combination chemotherapy, with the goal of preventing CNS involvement.

Several induction regimens are available. Currently, the HLH-94 [28] or HLH-2004 [23] protocols, which primarily target HLH-induced chemotherapy, are widely used. Other treatment options include DEP (liposomal doxorubicin + etoposide + methylprednisolone) [29] and DA-EPOCH (etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin) [30, 31]. Clinically, treatment regimens should be chosen based on the individual patient's condition.

Induction chemotherapy

HLH-94 protocol: The HLH-94 protocol includes etoposide, dexamethasone, cyclosporine, and intrathecal methotrexate. The frequency of etoposide administration is 1-2 times per week [32], with the dosage adjusted according to the patient's age, weight, and condition. For patients with liver or kidney damage, a dose reduction is recommended [33]. Dexamethasone is typically administered continuously for 8 weeks, with an initial dose of 10 mg/(m^2·d). The dose is halved every 2 weeks and is discontinued at week 8. In week 9, the dose is adjusted to 10 mg/(m^2·d) again, and a 2-week course is given from days 1-3. Cyclosporine is introduced at week 9, with a recommended dose of 6 mg/(kg·d) for patients with normal renal function (divided into 2 doses). For elderly patients with complications, the 2019 International HLH Society consensus suggests that the frequency of etoposide can be reduced to once a week, with a dose reduction from 150 mg/m^2 to 50-100 mg/m^2 [32].

HLH-2004 protocol: The HLH-2004 protocol is based on the HLH-94 protocol but advances the administration of cyclosporine to the first week, aiming to reduce patient mortality before hematopoietic stem cell transplantation and improve prognosis. However, clinical data show that early cyclosporine use increases the risk of treatment-related adverse reactions,

Table 3. HLH therapy

Sequential hematopoietic stem cell transplantation was performed after chemotherapy induced remission	
Induction scheme	Other treatments
HLH-94 or HLH-2004	DEP, DA-EPOCH
Clinical treatment should be individualized according to the specific conditions of patients	

DEP, Liposomal adriamycin + etoposide + methylprednisolone; DA-EPOCH, Etoposide + prednisolone + vincristine + cyclophosphamide + doxorubicin; HLH, hemophagocytic lympho histiocytosis.

such as significant increases in blood pressure and nervous system side effects [34]. As a result, HLH-2004 is no longer recommended as the first-line treatment for HLH. Additionally, since the clinical studies for HLH-94 and HLH-2004 were conducted primarily in juvenile patients (under 18 years of age), whether these protocols are effective for adult HLH patients remains to be confirmed by large-scale clinical studies.

DEP protocol: The DEP protocol is a three-drug combination chemotherapy regimen consisting of liposomal doxorubicin, etoposide, and methylprednisolone, first proposed by Wang et al. [29]. A dose-adjusted DEP regimen is recommended for LA-HLH patients [30]. The specific dosages are as follows: liposomal doxorubicin 35 mg/m^2·d-1 on day 1, etoposide 100 mg/m^2·d-1 on day 1, and methylprednisolone 2 mg/kg·d-1 on days 1-3, followed by 0.75 mg/kg·d-1 on days 4-7, 0.25 mg/kg·d-1 on days 8-10, and 0.1 mg/kg·d-1 until the next course of treatment. This regimen can be repeated every 2 weeks. When combined with ruxolitinib or L-asparaginase, the liposomal doxorubicin dose can be reduced to 25 mg/m^2 [3]. The DEP regimen is suitable for initial induction therapy in LA-HLH patients or for refractory cases that have failed HLH-94 treatment [3].

DA-EPOCH protocol: The DA-EPOCH protocol includes etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin for the treatment of HLH and non-Hodgkin lymphoma (NHL), with dosages tailored to the patient's condition. Studies show that the DA-EPOCH regimen is effective in treating B-NHL-related HLH, but it does not improve the prognosis of NK/T-NHL-related HLH patients [31]. Therefore, more effective treatments are needed for NK/T-NHL-related HLH (**Table 3**).

New drug research: With further understanding of HLH pathogenesis, researchers have identified several drugs that show promise for HLH patients, including Janus kinase (JAK) 1/2 inhibitors (ruxolitinib) [35, 36], IFN-γ inhibitors (ipilimumab) [37-39], CD52 monoclonal antibodies (alemtuzumab) [40], and IL-1 receptor antagonists (Anakinra) [41]. These treatments help control disease activity and may provide an opportunity for sequential hematopoietic stem cell transplantation.

Hematopoietic stem cell transplantation

The prognosis of LAHS patients receiving only chemotherapy is poor. Sequential hematopoietic stem cell transplantation (HSCT) after chemotherapy can prolong survival. Multiple studies have shown that certain LAHS patients achieve sustained complete remission (CR) and long-term survival following allogeneic HSCT (allo-HSCT) or autologous HSCT (auto-HSCT). HSCT should be performed as soon as clinical remission is achieved after chemotherapy. Transplantation during the active disease phase may significantly increase the risk of graft-versus-host disease due to cytokine storm [42, 43]. For LAHS patients in CR, auto-HSCT is a viable option. For those with partial remission (PR) or CR but with highly aggressive lymphoma, allo-HSCT should be considered [1].

Prognosis

LAHS is an aggressive disease with a poor prognosis. Studies indicate that patients who do not receive lymphoma-specific therapy have a very poor outcome, with nearly 30% dying within the first month after HLH diagnosis. This underscores the urgent need for combined HLH and lymphoma-specific therapies. The prognosis for LAHS patients is closely related to the type of lymphoma. A multicenter retrospective study in Japan found that patients with B-LAHS had a better prognosis than those with NK/T-LAHS [44]. A recent long-term retrospective study in Sweden, which included 307 adults and 9 children, reported that 52% of

cases were lymphoma-related, 29% were leukemia, 8% were other hematologic malignancies, and 11% were solid tumors. The overall 2-year survival rate was 25%. Among lymphoma patients, 2-year survival rates were 26% for B-cell lymphoma, 20% for lymphocytic leukemia, 16% for NK/T-cell lymphoma, and 13% for myeloid leukemia [45]. In terms of laboratory markers, NK cell activation is inhibited in HLH patients, while cytotoxic T lymphocytes and monocytes are abnormally activated, leading to elevated levels of IL-6, IL-8, and IL-10. Therefore, high levels of these cytokines are associated with poor prognosis [46]. Recent studies have suggested the ferritin/platelet ratio as a predictive indicator for induction therapy response in adult HLH patients [47]. Other risk factors for poor prognosis include hyperbilirubinemia [48], hypofibrinogenemia [49], and hypertriglyceridemia [50].

Summary

LAHS is a rare and complex disease that is difficult to diagnose early due to its nonspecific symptoms and lack of diagnostic markers. Even when diagnosed, patients often miss the optimal treatment window due to severe inflammation and multi-organ failure, resulting in high mortality. Therefore, improving early diagnosis, optimizing treatment strategies, balancing HLH and lymphoma treatments, and exploring more effective therapies are critical to improving patient survival and prognosis.

Acknowledgements

This study was funded by Shandong Provincial Natural Science Foundation (NO. ZR2021QH-319).

Disclosure of conflict of interest

None.

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