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ORIGINAL

Critical care management of patients with hemophagocytic lymphohistiocytosis

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Abstract *Objective:* Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition associated with multiple organ dysfunction. We sought to describe ICU management and outcomes in HLH patients meeting HLH-2004 criteria and to identify determinants of mortality. *Design:* Retrospective study between January 1998 and January 2009. *Setting:* Medical ICU of a teaching hospital. *Patients:* Among the 72 patients fulfilling the HLH-2004 criteria, we report the 56 patients with complete follow-up and no missing data. *Interventions:* None. *Measurements and main results:* Clinical and laboratory data were abstracted from the medical records. Median SOFA score at admission was 6.5 (IQR, 4–8). At ICU admission, the number of HLH-2004 criteria was 6 (5–7). Sixty-six precipitating factors were found in 52 patients and consisted of 43 tumoral causes (8 Castleman's diseases, 18 B cell lymphoma and 17 various malignancies), 13 non-viral infections and 10 viral infections. Underlying immune deficiency was present in 38 (67.8%) patients. Etoposide was used in 45 patients, corticosteroids in 31 and intravenous immunoglobulins in 3. Mechanical ventilation was required in 32 patients, vasoactive agents in 30 and renal replacement therapy in 19. Hospital mortality was 29/56 patients. By multivariate analysis, factors associated with increased hospital death were shock at ICU admission [OR, 4.33; 95% confidence interval (95% CI), 1.11–16.90; $P = 0.03$] and platelet count <30 g/l (OR, 4.75; 95% CI, 1.20–18.81; $P = 0.02$). B cell lymphoma [odds ratio (OR), 0.17; 95% CI, 0.04–0.80; $P = 0.02$] and Castleman's disease (OR, 0.11; 95% CI, 0.02–0.90; $P = 0.04$) were associated with increased hospital survival. *Conclusions:* Aggressive supportive care combined with specific treatment of the precipitating factor can produce meaningful survival in patients with HLH responsible for multiple organ failures. Survival is highest in patients with HLH related to Castleman's disease or B cell lymphoma.

Keywords Macrophage activation · Histiocytosis · Outcomes assessment · Autoimmune diseases · Multiple organ failure

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder in which dysregulation of natural killer (NK) cells and cytotoxic T cells can lead to multiple organ failure [1, 2]. Uncontrolled activation and proliferation of lymphocytes and/or histiocytes occurs, leading to cytokine overproduction and hemophagocytosis [3].

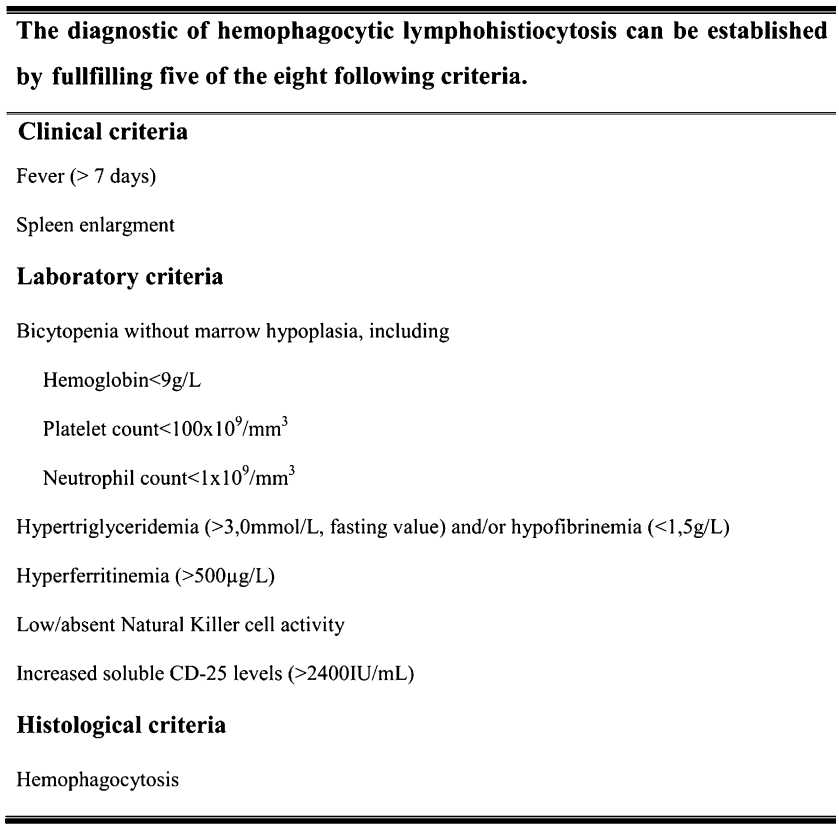

Fig. 1 Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH) as established in the HLH-2004 protocol of the Histiocyte Society. HLH diagnosis can be established by fulfilling five of the eight proposed criteria

The main manifestations are a fever, enlargement of the liver and spleen, cytopenias (anemia, thrombocytopenia and leukopenia), liver dysfunction, high serum levels of triglycerides and ferritin, and histological evidence of hemophagocytosis [4, 5].

Beyond controversies about primary and secondary HLH [6], HLH in adults is a syndrome that can occur in all age groups in association with many diseases, including malignancies, connective tissue disease, infections and genetic abnormalities [7, 8]. Of the various criteria sets for the diagnosis of HLH [4, 9, 10], the most widely used was developed in 2004 by the Histiocyte Society [3, 4] and requires five of the eight criteria that are mentioned in Fig. 1. In addition to these criteria, a diagnosis of HLH is supported by the identification of a precipitating factor (e.g., infection, autoimmune disease or malignancy) and by the presence of immune deficiency.

HLH is associated with a broad spectrum of clinical manifestations and multiple organ dysfunctions that can require admission to the intensive care unit (ICU) [2, 11]. Autopsy studies suggest that HLH may be under-recognized in ICU patients [12]. On the other hand, HLH may be mistakenly diagnosed in patients with septic shock, a condition whose cause and symptoms overlap those of HLH [13]. Studies in critically ill patients with sepsis and cytopenia but no HLH found hemophagocytosis and macrophage activation in bone marrow smears in 0.8% and 4% of cases, respectively [10, 13]. However, these data are difficult to interpret as no cytological results from a relevant control population were available.

HLH was fatal in 22–59% of patients in previous studies [9, 14, 15]. Mortality rates were higher when the precipitating factor was a malignancy or Epstein-Barr virus (EBV) infection, as opposed to other infections (with viruses or intracellular bacteria) [14]. The most common causes of death were multiple organ failure, bleeding and sepsis [14]. Few studies assessed the factors associated with mortality in HLH patients, and none were conducted in ICU patients. Moreover, for HLH related to EBV infection, new therapy with etoposide initiation within 4 weeks of the diagnosis was associated with 90% long-term survival, compared to 56% when etoposide was started later [16]. However, none of these patients were described as having multiple organ dysfunction. To the best of our knowledge, there are no available data on outcomes of critically ill patients with HLH.

Here, our objective was to assess the features, ICU management and outcomes of critically ill patients with HLH, and to identify factors associated with mortality.

Patients and methods

We conducted a retrospective study in all adults who were admitted to the medical ICU of the Saint Louis Teaching Hospital between January 1998 and January 2009 and who met the HLH-2004 criteria for HLH. Hemophagocytosis was defined as histological evidence of activated macrophages engulfing erythrocytes, leukocytes, platelets and their precursor cells in bone marrow smears or biopsies and/or in liver or spleen biopsies (Fig. 2). All patients were managed jointly by the ICU team and a hematologist-immunologist consultant. All survivors were discharged from the ICU to the department of clinical immunology in the same hospital. In patients admitted to the ICU more than once during the study period, only the first admission was included in the study. Our institutional review board approved the study and waived the need for informed consent.

The study data (Table 1) were abstracted from the medical records. Castleman's disease (or angiofollicular lymphoid hyperplasia) is a non-cancerous proliferation of lymph nodes associated with inflammatory symptoms and interleukin 6 (IL-6) dysregulation. In the context of human immunodeficiency virus (HIV) infection, multicenter Castleman's disease is associated with Kaposi sarcoma-associated herpesvirus type 8 (KSHV/HHV8). Performance status was measured as previously reported [17]. The diagnosis of HIV infection was based on positive ELISA and Western blot tests before or during the ICU stay. Organ dysfunction was assessed at admission then on days 1, 3 and 5 using the Sequential Organ Failure Assessment (SOFA) score [18]. All patients received full-code management. The use of etoposide and other anticancer agents was recorded. Vital status at ICU and hospital discharge was available for all patients.

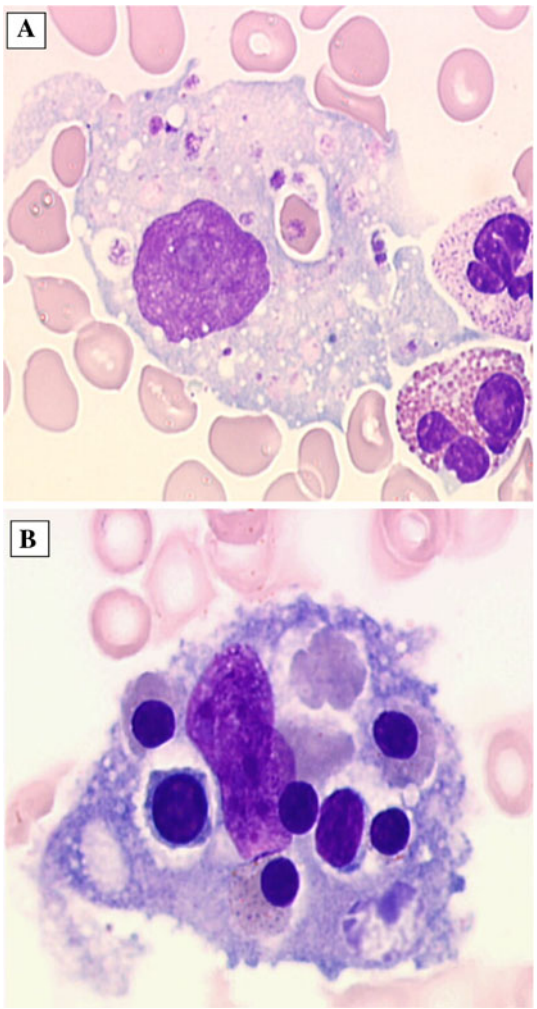

Fig. 2 Histological evidence of hemophagocytosis. **a** Hematoxylin-eosin stain of bone marrow showing histiocytes phagocytizing erythroblasts and lymphocytes. **b** Hematoxylin-eosin stain of bone marrow showing phagocytic cells containing erythrocytes and platelets

Statistical analysis

Results are reported as median (interquartile range) or number (%), unless stated otherwise. Patient characteristics were compared using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the Wilcoxon or Kruskal-Wallis test, as appropriate, for continuous variables. Associations linking patient characteristics (variables in Tables 1, 2) to hospital mortality were assessed using a logistic regression model. Multivariable analysis was performed using a forward stepwise selection procedure. In the first step, all variables associated with hospital mortality in the univariate analysis were entered into the model. Entered variables were dropped if they were no longer significant when other variables were added. Variables entered into the final model are listed in the Table 4 footnote. Odds ratios (ORs) and their 95% confidence intervals (95%CI) were computed. Kaplan-Meier survival curves were plotted over the follow-up period. All tests were two-sided, and P values less than 0.05 were considered statistically significant. Analyses were done using the Statview 5.0 software package (SAS Institute, Cary, NC) on a personal computer.

Results

During the study period, 5,027 patients were admitted to our medical ICU. Among them, 528 patients had bone marrow examinations that provided pictures of hemophagocytosis in 71 (13.5) cases. As shown in Fig. 3,

Table 1 Patient characteristics at baseline, symptoms, precipitating factors and underlying immune deficiency in ICU patients with hemophagocytic lymphohistiocytosis (HLH)

Variable	*n* (%) or medians [IQR]
Demographics	
Age, years	49 [30–73]
Male gender	43 (76.8)
Co-morbidities	
Viral hepatitis	10 (17.9)
Hypertension	11 (19.6)
Diabetes	5 (8.9)
Chronic heart failure	5 (8.9)
Autoimmune disease	7 (12.5)
Immune deficiency	
Malignancies[a]	26 (46.4)
HIV positive	18 (32.1)
Immunosuppressive medications	6 (10.7)
Prior history of HLH	3 (5.3)
Time from hospital to ICU admission, days	10 [4–21]
Reasons for ICU admission	
Acute respiratory failure	17 (30.3)
Coma, confusion	12 (21.4)
Shock	10 (17.8)
Acute renal failure	9 (16.1)
Fulminant liver failure	5 (7.1)
Acute bleeding	3 (5.3)
SOFA score at ICU admission	6.5 [4–8]
HLH-related symptoms	
Clinical criteria	
Body temperature (°C)	39.7 [38.5–40.0]
Spleen enlargement (physical exam and echography), *n* (%)	43 (76.8)
Laboratory criteria	
Hemoglobin (g/dl)	8.3 [7.4–9.5]
Platelet count ($\times 10^9$/mm^3)	2.9 [1.9–5.0]
Neutrophil count ($\times 10^9$/mm^3)	3.4 [1.8–8.4]
Triglycerides (mmol/l)	2.65 [1.93–4.3]
Ferritin (μg/l)	5,219 [2,752–10,000]
Fibrinogen (g/l)	2.6 [1.7–4.5]
Histological evidence of hemophagocytosis, *n* of patients (%)	44 (78.6)
Total number of diagnostic criteria	6.0 [5–7]
Precipitating factors, *n* (%) (72 factors in 56 patients)	
Undetermined	4 (7.1)
Tumoral diseases[b]	43 (76.8)
Castleman's disease[c]	8
B cell lymphoma	18
Other malignant diseases	17
Non-viral infection	13 (23.2)
Tuberculosis	6
Blood stream infections	5
Toxoplasmosis (1 case in B cell lymphoma patient)	4
Viral infections	10 (17.9)
Herpes simplex reactivation associated with	1
B cell lymphoma	
Autoimmune disease (Kikuchi disease)	1
CMV reactivation associated with	
Castleman's disease	1
B cell lymphoma	2
Reactivation of both HSV and CMV infections	
Castleman's disease	3
B cell lymphoma	1
Hodgkin's disease	1
Underlying immune deficiency	
HIV infection	18 (32.1)
Immunosuppressive agents	20 (35.7)
Including corticosteroids	14 (25.0)

HLH hemophagocytic lymphohistiocytosis, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit, *HIV* human immunodeficiency virus

[a] Nineteen of the 26 malignancies had been previously diagnosed, and 7 were at the earliest phase (before any therapy) but diagnosed before ICU admission

[b] Sixteen patients had two precipitating conditions; five patients had blood stream infections associated with B cell lymphoma ($n = 3$) and T cell lymphoma ($n = 2$); three patients had tuberculosis with Hodgkin's disease, B cell lymphoma and Castleman's disease; eight viral infections occurred in patients with tumoral diseases

[c] Castleman's disease (or angiofollicular lymphoid hyperplasia) is a non-cancerous proliferation of lymph nodes associated with inflammatory symptoms and interleukin 6 (IL-6) dysregulation. In the context of human immunodeficiency virus (HIV) infection, multicenter Castleman' disease is associated with Kaposi sarcoma-associated herpesvirus type 8 (KSHV/HHV8)

among the 102 patients who met the HLH criteria, 27 had pictures of hemophagocytosis but did not meet the HLH-2004 criteria. Reasons for not meeting the criteria are reported in Fig. 3. Complete follow-up data were available for 56 of the remaining 75 patients. These 56 patients form the basis for this study.

The main patient characteristics at baseline are reported in Table 1. The median SOFA score was 6.5 (4–8), indicating that most patients had severe failure of at least two organs. HLH was diagnosed before ICU admission in 32 patients and during the ICU stay in 24 (43%) patients. The time from diagnosis to ICU admission was 10 days (4–20) in the 32 diagnosed before the ICU. Reasons for ICU admission were acute respiratory failure in 17 (30.3%) patients, coma or confusion in 12 (21.4%), shock in 10 (17.8%), acute renal failure in 9 (16.1%), fulminant liver failure in 5 (7.1%) and acute bleeding in 3 (5.3%). At ICU admission, 7 (12.5%) patients had a known history of connective tissue disease and 26 (46.4%) of malignancy. Furthermore, three (5.3%) patients had a prior history of HLH. Performance status indicated no or mild limitation in 37 (66%) patients.

Table 2 lists the manifestations of HLH in the study patients. At ICU admission, the number of HLH-2004 criteria was 6 (5–7). A fever (>37.8°C) was present in 37 (66.1%) patients, cytopenia of at least one line in 54 (96.4%), alanine aminotransferase elevation to more than twice the upper limit of normal in 23 (41.2%), and serum

Table 2 Life-supporting treatments, investigations and adjuvant treatments for hemophagocytic lymphohistiocytosis during the intensive care unit stay and outcome

Characteristic	*n* (%) or median [IQR]
Mechanical ventilation	32 (58.2)
Vasoactive drugs	30 (53.6)
Renal replacement therapy	19 (33.9)
Bone marrow examination	49 (87.5)
Nosocomial infection	13 (23.2)
Antibacterial treatment	46 (82.8)
Antifungal therapy	17 (30.3)
Antituberculous treatment	9 (16.1)
Antiviral therapy	10 (17.8)
Corticosteroids	31 (55.4)
Intravenous immunoglobulins	3 (5.3)
Etoposide	45 (80.3)
Anticancer chemotherapy	32 (57.1)
Splenectomy	4 (7.4)
Time to etoposide initiation (hours)	5 [2–14]
ICU length of stay (days)	8.5 [3.7–12.5]
Hospital length of stay (days)	23.5 [11.2–41.7]
Death in the ICU	22 (39.2)
Death in the hospital	29 (51.8)

sodium lower than 135 mmol/l in 40 (71.4%). As reported in Table 2, the main precipitating factors were tumoral causes ($n = 43$, 76.8%), including 17 that were newly diagnosed, non-viral infections ($n = 13$, 23.2%) and viral infections in 10 (17.9%) patients. In four (7.1%) patients, no precipitating factor was found. Among the 43 patients with tumoral diseases, 18 patients were diagnosed with B cell lymphoma, 8 with Castleman's disease and 17 with various types of malignancies. The search for a cause of immune deficiency identified HIV infection in 18 patients, and 20 were taking immunosuppressive medications. Table 3 reports the main abnormalities at ICU admission. For diagnostic purpose, bone marrow smears were performed in 49 of the 56 patients, bone marrow biopsies in 2, liver biopsies in 12 and diagnostic splenectomy in 4. Etoposide was used in 45 patients, corticosteroids in 31 (55.4%) and intravenous immune globulins in 3. The time from ICU admission to the first etoposide dose was 5 (2–14) h. Cancer chemotherapy was given to 32 patients. Life-sustaining treatments included mechanical ventilation in 32 patients, vasoactive agents in 30 and renal replacement therapy in 19 (Table 4). Antimicrobial agents were used in 46 patients and blood transfusions in 41 (73.2%).

Of the 56 patients, 22 (39.2%) died in the ICU, and 7 others died before hospital discharge (29/56, 51.8%). Differences between hospital survivors and nonsurvivors are reported in Table 3. By univariate analysis, SOFA scores on days 0 and 3 were significantly higher in nonsurvivors than in survivors ($P < 0.001$ and $P = 0.05$, respectively; Fig. 4). Of the four factors that independently predicted hospital mortality in the multivariate analysis (Table 4), two were associated with increased mortality: shock at ICU admission (OR, 4.33; 95% CI, 1.11–16.90; $P = 0.03$) and platelet count <30 g/l (OR, 4.75; 95% CI, 1.20–18.81; $P = 0.02$). The two factors that had protective effects were Castleman's disease (OR, 0.11; 95% CI, 0.02–0.90; $P = 0.04$) and diagnosis of B cell lymphoma (OR, 0.17; 95% CI, 0.04–0.80; $P = 0.02$).

Discussion

We describe the characteristics of adults with early stage HLH who met the HLH-2004 diagnostic criteria and who required ICU admission for the diagnosis and management of multiple acute organ failures. A precipitating factor was identified in 93% of patients, and about half the patients had a readily identifiable cause of

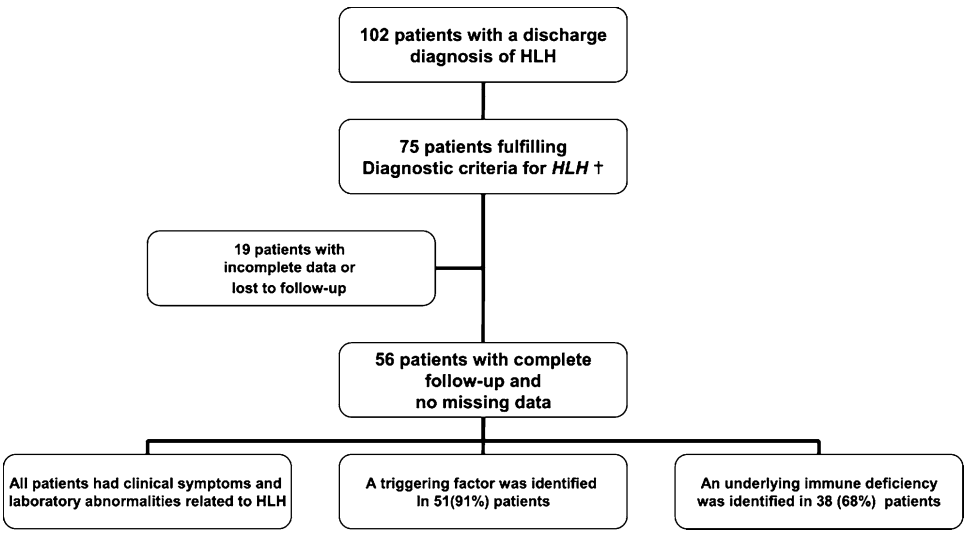

Fig. 3 Patient flow chart. †Twenty-seven patients had pictures of macrophage activation and were coded as HLH patients but did not fulfill the HLH 2004 criteria. Indeed, none of them had cytopenia, elevated triglycerides or ferritinemia

Table 3 Comparison of survivors and nonsurvivors

Patients characteristics, $n = 56$ patients	Non-survivors, $n = 29$ (%)	Survivors $n = 27$ (%)	P value
Age, years	50 [36–60]	48 [35–60]	0.91
Male gender	22 (75.8)	21 (77.8)	0.86
Number of comorbid conditions[a]	0 [0–1]	0 [0–1]	0.63
Previous history of malignant disease	21 (72.4)	22 (81.5)	0.42
Time from hospital to ICU admission, days	12 [4–17]	10 [2–23]	0.94
SOFA			
Day 0	8 [5–10]	5 [2–7]	0.001
Day 3	12 [9–17]	7 [3–12]	0.05
Day 7	4 [2–7.5]	9.5 [8–13]	0.02
Temperature	39.5 [38.5–40]	39.8 [38.6–40.0]	0.70
Spleen enlargement	22 (75.8)	21 (77.7)	0.86
Platelet count ($\times 10^{12}$/mm^3)	27 [13–34]	38 [26–71]	0.05
Hemoglobin (g/dl)	8.4 [7.5–9.5]	8.3 [7.4–9.7]	0.80
Leucocytes (10^9/mm^3)	3,500 [1,700–11,000]	3,300 [1,200–8,200]	0.33
Ferritin (μg/l)	6,300 [2,700–10,000]	4,500 [2,700–7,700]	0.66
Triglycerides (mmol/l)	2.9 [2.2–4.3]	2.6 [1.8–4.3]	0.43
Hemophagocytosis (histology or cytology)	26 (89.6)	18 (66.6)	0.04
Reasons for ICU admission			
Shock[b]	21 (72.4)	13 (48.1)	0.04
Acute respiratory failure	10 (34.5)	7 (25.9)	0.80
Acute kidney injury	4 (13.8)	5 (18.5)	0.90
Confusion/coma	7 (24.1)	5 (18.5)	0.90
Fulminant hepatitis	4 (13.8)	1 (3.1)	0.30
Life-sustaining therapies			
Mechanical ventilation	21 (72.4)	11 (40.7)	0.01
Vasopressors	21 (72.4)	9 (33.3)	0.004
Renal replacement therapy	14 (48.2)	5 (18.5)	0.02
HLH etiologies			
Undetermined	3 (10.3)	1 (3.7)	0.32
Castleman's disease[c]	2 (6.9)	6 (22.2)	0.09
B cell lymphoma[c]	6 (20.7)	12 (44.5)	0.05
Other malignancy[c]	11 (37.9)	6 (22.2)	0.27
HLH-related to non-viral infections	8 (27.6)	5 (18.5)	0.53
HLH related to viral infections	6 (20.7)	4 (14.8)	0.73
Specific HLH therapies			
Steroids	14 (48.2)	17 (62.9)	0.41
Intravenous immunoglobulins	2 (6.9)	1 (3.7)	0.90
Time from admission to etoposide, hours	6 [2–24]	4 [2–15]	0.19
Splenectomy	2 (6.9)	2 (7.4)	0.90
Chemotherapy	17 (58.6)	15 (55.6)	0.90

SOFA Sequential Organ Failure Assessment

[a] Comorbid conditions included hypertension, COPD, chronic cardiac or renal insufficiency, diabetes, chronic B or C hepatitis and cirrhosis. The score that is mentioned is the sum of all comorbidities

[b] Hypotension was defined as a systolic blood pressure below 85 mmHg

[c] Among the 45 malignant diseases (Castleman's disease, B cell lymphoma and other malignancies), 26 were diagnosed prior to ICU admission

immunosuppression. With etoposide-based therapy, treatment of precipitating factors and full-code life-supporting treatment, hospital mortality was 51.8%. Factors that independently influenced hospital mortality were admission to the ICU for shock and thrombocytopenia <30 g/l. Castleman's disease and B cell lymphoma were precipitating factors associated with decreased hospital mortality. Etoposide (VP-16) is a cytotoxic drug that selectively targets the monocyte line through the enzyme topoisomerase-2. Etoposide and steroids comprise an immunochemotherapy that benefits patients with HLH [16, 29]. It acts rapidly, within 24–48 h. Its efficacy far outweighs the risk of secondary leukemia and transient worsening of the neutropenia.

It is of major importance for critical care physicians to be aware that pictures of hemophagocytosis can be encountered during sepsis [6, 13] or multiple organ failure [19], and that HLH and sepsis-associated hemophagocytosis may overlap, share common features and may not be reliably discriminated by the diagnostic criteria of HLH. Usually, sepsis-induced thrombocytopenia is mostly related to peripheral consumption such as DIC or pulmonary

Table 4 Predictors of hospital mortality by multivariable analysis

Variable	Odds ratio	95% CI	*P* value
ICU admission for shock	4.33	1.11–16.90	0.03
Platelet count <30 g/l	4.75	1.20–18.81	0.02
Diagnosis of B cell lymphoma	0.17	0.04–0.80	0.02
Castleman's disease	0.11	0.02–0.90	0.04

The following variables were entered in the multivariate model: First hemophagocytosis, thrombocytopenia and ICU admission for shock were introduced in the model. Since hemophagocytosis was dropped by the model, we then entered Castleman's disease and B cell lymphoma. Last, etoposide administration was forced in the model to be consistent with the literature

Goodness of fit (Hossmer Lemeshow chi-square *P* value) = 0.22

95% CI 95% confidence interval

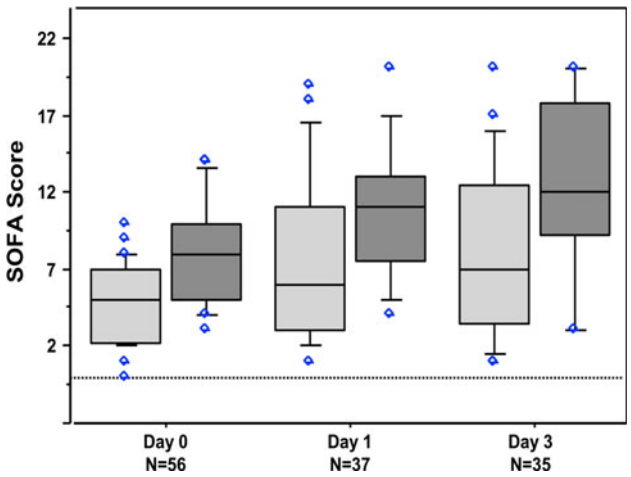

Fig. 4 Sequential SOFA score assessment according to vital status at hospital discharge. Survivors are in *light gray* and nonsurvivors in *dark gray*. *Box plots* indicate the median and the 5th and 95th percentiles. *P* values < 0.01 for all comparisons between survivors and nonsurvivors using the Mann-Whitney test

sequestration. Nonetheless, in septic patients, impaired platelet production by medullar hemophagocytosis may contribute to thrombocytopenia [20–23]. However, the potential link with macrophage dysregulation and cytokine imbalance still seems to be unclear in the setting of sepsis-induced immunosuppressive response. In HLH, the primary abnormality is cytokine-driven macrophage activation against a background of preexisting immune deficiency leading to hemophagocytosis and organ dysfunction [7].

We identified two factors that were associated with increased short time survival, Castleman's disease and B cell lymphoma. Castleman's disease related to human herpesvirus 8 infection and Kaposi's sarcoma is known to be associated with HLH [24]. In patients with Castleman's disease, etoposide has been reported to ensure the prompt resolution of HLH [25, 26]. Conceivably, anticancer chemotherapy may be effective in resolving HLH associated with malignancies. Therefore, we suppose that HLH associated with lymphoma may be more responsive to chemotherapy with quickly resolving organ dysfunctions. Shock at ICU admission was associated with a higher rate of hospital mortality in our study. This finding is consistent with data from patients with sepsis showing that a greater number of organ failures is associated with a higher mortality rate [27].

Our study has several limitations. First, the cohort was recruited at a single center. Nevertheless, our ICU has extensive experience in the management of patients with hematological malignancies, and we work in close collaboration with the hematologists at our hospital [17, 28]. HLH is an uncommon syndrome that is best managed at centers caring for large numbers of hematology patients. Thus, our ICU is representative of the appropriate setting for managing HLH patients. Second, we used a retrospective design. However, over the 11-year study period the senior physicians at our ICU and hematology departments remained the same and used the same standardized approach to the management of HLH. Furthermore, the medical records contained reliable information on all the pre-defined study variables. Third, throughout the study period patient's management may have changed. However, we did not identify any changes over time in ICU management and/or treatments for precipitating factors such as hematological malignancies. Finally, two-thirds of our patients had hematological malignancies, compared to only 41% with infections and one patient with autoimmune disease. These data are difficult to compare to the literature since no case series of non-selected ICU patients with HLH are available. Whether our findings can be generalized to cohorts characterized by different distributions of precipitating factors is unclear.

In summary, even when HLH is responsible for multiple organ failures requiring ICU admission, aggressive supportive care combined with treatment of the precipitating factor ensures the survival of nearly half the patients. The chances of short-term survival are particularly high in patients with Castleman's disease or B cell lymphoma, possibly related to sensitivity to cancer chemotherapy.

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