Features of hemophagocytic lymphohistiocytosis in the intensive care unit (ICU) : a 260-patient retrospective analysis

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Research

Keywords: Hemophagocytic lymphohistiocytosis, macrophage activation syndrome, hemophagocytosis, cytokine storm, intensive care unit

Posted Date: March 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-348702/v1

Abstract

Background

Adult hemophagocytic lymphohistiocytosis (HLH) is highly lethal in the ICU. The diagnostic and therapeutic emergency that HLH represents is compounded by its unknown pathophysiological mechanisms. Here, we report on a large cohort of adult-acquired HLH in the ICU. We analyzed prognostic factors associated with mortality to define the diagnostic and therapeutic challenges in this specific population,

Methods

This retrospective study included adult patients diagnosed with HLH in four ICUs in Marseille, France between 2010 and 2020. Patients who fulfilled the HLH-2004 criteria (> 4/8) and/or had an HScore > 169 were diagnosed with HLH. HLH was categorized into four groups according to etiology: sepsis-associated HLH, intracellular infection-associated HLH, malignancy-associated HLH, and idiopathic HLH.

Results

260 patients were included: 121 sepsis-associated HLH (47%), 84 intracellular infection-associated HLH (32%), 28 malignancy-associated HLH (11%), and 27 idiopathic HLH (10%). The ICU mortality rate reached 57% (n = 147/260) without a statistical difference between etiological groups. Independent factors associated with mortality in multivariate analysis included age (OR (5 years) = 1.31 [1.16–1.48], p < 0.0001), SOFA score at ICU admission (OR = 1.37 [1.21–1.56], p < 0.0001), degradation of the SOFA score between ICU arrival and HLH diagnosis (Delta SOFA) (OR = 1.47 [1.28–1.70], p < 0.0001), the presence of bone-marrow hemophagocytosis (OR = 5.27 [1.11–24.97], p = 0.04), highly severe anemia (OR = 1.44 [1.09–1.91], p = 0.01), and hypofibrinogenemia (OR = 1.21 [1.04–1.41], p = 0.02).

Conclusions

In this large retrospective cohort study of critically ill patients, ICU-acquired HLH in adults was associated with a 57% mortality rate, regardless of HLH etiology. Factors independently associated with prognosis included age, presence of hemophagocytosis in bone-marrow aspirates, organ failure at admission, and worsening organ failure during the ICU stay. Whether a rapid diagnosis and the efficacy of specific therapy improve outcome is yet to be prospectively investigated.

Introduction

Adult hemophagocytic lymphohistiocytosis (HLH) can be defined as the most extreme form of the inflammatory process continuum. Imbalances in or a failure of feedback between pro- and anti-

inflammatory pathways in response to a trigger lead to uncontrolled macrophage/monocyte and lymphocyte activation and proliferation [1]. A sustained cytokine storm may complicate HLH syndrome, ultimately leading to multiorgan dysfunction (MODS) [2, 3]. Diagnostic criteria for HLH include clinical parameters (fever, adenopathy, splenomegaly, hepatomegaly) and biological variables (cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia), although these criteria are non specific and may be inappropriate, as they are extrapolated from the pediatric population [4]. Pediatric primary HLH is mostly caused by genetic mutations in genes involved in lymphocyte cytotoxicity [5–8]. In contrast, the analysis of adult HLH has highlighted the absence of a lymphocyte cytotoxicity defect [9].

As adult-onset HLH constitutes a post-trigger inflammatory process, pathophysiological clusters can be described, mirroring their etiology [10, 11]: infection-associated HLH (bacteria, Herpesviridae, mycobacteria, parasites, fungi), malignancy-associated HLH, and systemic auto-immune/inflammatory-disease-associated HLH (systemic erythematosus lupus, juvenile chronic arthritis, adult Still disease), the latter still defined as macrophage-activation syndrome [1, 10]. Careful etiological diagnosis must be performed promptly, as it has a large influence on the prognosis and defines treatment [12]. Understanding the pathophysiology underlying HLH is the key to cytokine-storm and/or cellular-proliferation targeted therapy [13, 14].

The diagnosis of HLH in ICU patients is often difficult, presenting as “hyper-inflammatory sepsis” [15]. Sepsis is often described as the trigger for HLH in ICU patients [16, 17]. Without any obvious etiology, such as cancer, the diagnosis of acquired HLH leads to uncertainty concerning the decision to initiate specific treatment. Therapy for ICU-acquired adult HLH mainly involves standard organ support, thorough etiological screening, and urgent treatment of the HLH trigger (infection, auto-immune underlying condition, malignant process). “Specific” HLH therapies (corticosteroids, polyvalent immunoglobulins, anti-cytokine therapies, etoposide) are often solely administered in the severest cases of ICU-acquired adult HLH. Targeted therapy is based on the HLH-2004 protocol [18–19]. However, acquired adult HLH and primitive pediatric HLH are two different diseases, with non-comparable pathophysiology [9]. In addition, systematic immunosuppressive therapy on fragile ICU patients could aggravate their condition and expose them to a high risk of infection [20].

We aimed to describe the epidemiological, clinical, and biological characteristics of ICU-acquired HLH in adults according to etiological cluster to better understand the disease and aid in its rapid diagnosis and delivery of appropriate treatment. By defining the prognostic factors associated with ICU mortality, we focus on patients for whom their condition constitutes a diagnostic and therapeutic emergency.

Methods

We performed a retrospective observational multi-institutional study for patients admitted to the ICU’s of the European Hospital, Timone University Hospital, and Nord University Hospital and the Onco-Hematological ICU of the Paoli-Calmette Institute, in Marseille, France between January 2010 and June 2020. The medical information department (DIM) of each hospital provided the cohort using the

following keywords: “hemophagocytosis”, “hemophagocytic lymphohistiocytosis”, “macrophage-activation syndrome” and “hyperferritinemia”. Only adult patients with ICU-acquired HLH were included among the selected files. An HLH diagnosis required fulfilment of at least 4 of 8 HLH-2004 criteria (95% sensitivity and 93.6% specificity for ICU adult patients [21]) and/or an HScore > 169 (93% sensitivity and 86% specificity [22]). This study was communicated to the Commission on Data Processing and Freedom representative of each center and approved by APHM ethic committee (#2019 – 316).
Immunosuppression was reported for stem-cell or solid-organ transplantation, solid-organ cancer, hematological disease, chemotherapy administration within six months prior to ICU admission, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), and long-term immunosuppressive treatment (including steroids). Severity was assessed using the Sepsis-related Organ Failure Assessment (SOFA) score, ranging from 0 to 24, with higher scores indicating a higher severity of organ failure [23], at ICU admission and again at HLH diagnosis (defined as the day of bone-marrow aspiration or ferritin measurement). The Delta SOFA score was obtained by subtracting the SOFA score at HLH diagnosis from that at ICU admission.

Patients were classified into four main groups based on HLH etiology: sepsis-related HLH (bacterial, extracellular bacteria, or fungal infection), intracellular infection-related HLH (*Herpesviridae*, COVID-19, influenza, mycobacteria, or pneumocytosis), malignancy-related HLH (active solid cancer or ongoing malignant hemopathy), or idiopathic HLH (patients with acquired and etiologically unexplained HLH). Sepsis-related HLH (extracellular bacteria and fungi) was distinguished from intracellular bacterial infection-related HLH, as the latter leads to different immunological and pathophysiological patterns [24]. In addition, intracellular infections are rarely associated with sepsis and are believed to lead to a more specific prognosis. Epstein-Barr Virus (EBV)-associated HLH was retained for patients with a concomitant positive serum EBV polymerase chain reaction (PCR) and HLH diagnosis. Malignancy-related HLH concerned patients who were newly diagnosed with cancer or who relapsed at HLH diagnosis, without concomitant infection. None of the reported cases of HLH were attributed to systemic or auto-immune disease.

After describing the overall population, we compared populations according to their main etiology using the Chi² test (or Fisher exact test) for qualitative variables and analysis of variance (ANOVA - corrected using the Welch method if the variances were inequal between groups) for quantitative variables, followed by a Bonferoni *post-hoc* test.

We analyzed ICU mortality risk factors using univariate and multivariate logistic regression analyses. A 0.20 alpha threshold of significance in univariate analysis was set. Backward variable elimination was then performed to determine factors significantly associated with ICU mortality in multivariate analysis, using a 0.05 threshold for the p-value. The main etiology was forced into the model. The Hosmer-Lemeshow test was then used to evaluate the goodness of fit of the model. Quantitative variables are described using medians, with the 25% and 75% interquartile ranges (IQR 25%-75%), and qualitative variables using frequencies and percentages. All statistical analyses were performed using SAS 9.4 software. A p value < 0.05 was considered significant.

Results

In total, 260 patients were included from 340 screened files over a 10-year inclusion period (Fig. 1). Patient characteristics are presented in Table 1. The median age was 60 years [50–69], with a male predominance (sex ratio 2.25/1). Most of the patients were immunosuppressed (n = 165, 64%). The median SOFA score at ICU admission was 9 [7–11]. The main HLH trigger was infections: 47% sepsis related-HLH (n = 121: 102 extracellular bacteria and 19 fungi – details in **Additional File 1**) and 32% intracellular infection-related HLH (n = 84: 59 Herpesviridae, 9 influenzae virus, 8 COVID-19, 4 pneumocystis, and 4 mycobacteria). Malignancy-related HLH accounted for 11% of the cases (n = 28: 14 non-Hodgkin lymphoma (NHL), 6 solid-organ cancers, 5 acute myeloid leukemia (AML), 2 EBV-associated NHL, and 1 multiple myeloma (MM)) and idiopathic HLH 10% (n = 27). The median HScore was 200 [176–230], corresponding to an 88% [65–98] probability of HLH. A median of five HLH-2004 criteria [4–5] were fulfilled. Bone marrow hemophagocytosis was reported for 91% of patients (n = 237). Steroids were used to treat 54% of patients (n = 141), whereas other HLH-related treatments (etoposide, ciclosporin A) were exceptionally used. ICU mortality was 57% (n = 147), with a median length of stay of 23 days [IQR 13–41]. Six-month survival was 28% (n = 72).

Table 1
Characteristics of the 260 HLH patients in ICU

PATIENTS	NUMBER n = 260	PERCENTAGE
AGE (years)	60 [50–69]	-
GENDER (M/F)	2.25/1	-
PRIOR IMMUNOSUPPRESSION	165	64
SEVERITY ASSESSMENT		
SOFA at ICU admission	9 [7–11]	-
Delta SOFA	3 [1–5]	-
HLH ETIOLOGY	-	-
Sepsis related-HLH	121	47
Intracellular infections related-HLH	84	32
Malignancy related-HLH	28	11
Idiopathic HLH	27	10
HLH BIOLOGY	-	-
Hemoglobin, g/dL	8.3 [7.6-9]	-
Platelets, G/L	34 [15–58]	-
Neutrophils, G/L	5 [1.7–11.7]	-
Fibrinogen, g/L	4.1 [2.4-6]	-
Ferritin, µg/L	2677 [1325–5191]	-
Triglycerides, g/L	2.6 [1.8-4]	-
LDH, UI/L	493 [311–985]	-
BONE MARROW ASPIRATION		-
Positive (HmP)	237	91
Negative (no HmP)	13	5
Unavailable	10	4
HLH DIAGNOSTIC CRITERIA		
HScore	200 [176–230]	-
HLH probability with HScore	-	88 [65–98]

PATIENTS	NUMBER n = 260	PERCENTAGE
HLH-2004 criteria	5 [4–5]	-
HLH TREATMENT		
Steroids	141	54
Ciclosporin A	15	6
Intravenous immunoglobulin	17	6
Etoposide	21	8
OUTCOMES		
ICU length of stay, days	23 [13–41]	-
ICU mortality	147	57
6-month survival	72	28

The clinical and biological criteria according to the main HLH etiology are presented in Table 2. Immunosuppression was more frequent for malignancy-related HLH patients (n = 27/28, 96%, p < 0.001). Analysis of the ICU severity score showed a significantly higher SOFA score (9 [7–12], p = 0.04) for sepsis-related HLH patients. The Delta SOFA did not significantly differ between the main groups. Cytopenia was significantly more pronounced in malignancy-related HLH, with more profound anemia (hemoglobin = 7.9 g/dL [7.5–8.7], p = 0.49), neutropenia (neutrophils = 3 G/L[1.3–6.4], p = 0.39), and thrombopenia (platelets = 32 G/L [11–49], p = 0.03), except when compared to the sepsis related-HLH group. Malignancy-related HLH patients showed markedly higher HLH biomarker levels, with lower fibrinogen (2.4 g/L [1.8–5.2], p = 0.001) and higher ferritin levels (5128 µg/L [3029–6842], p = 0.14), and subsequently higher HScores (239 [213–270]) and a higher probability of HLH (99% [94–99], p = 0.051). Only four patients lacked the ferritin measurement at HLH diagnosis, but had an HScore > 169 (185 [74.65% probability], 184 [73.5% probability], 182 [70.9% probability], and 223 [96.88% probability]). When treated, HLH-specific therapy was introduced within a 2-day [1–8] period, the timeline being longer for idiopathic HLH than for the other etiologies (12 [8–16], p < 0.001). Sepsis-related HLH patients received steroids less often than the others (n = 51 (42%), p = 0.002) and less anti-proliferative therapy (for etoposide, n = 6 (5%)) than patients with malignancy-related HLH (n = 5 (18%), p = 0.13). ICU mortality was the highest among patients with malignancy-related HLH (n = 17/28 (61%), p = 0.59) and the lowest for the sepsis group (n = 64/121 (53%), p = 0.59).

Table 2
Patient characteristics according HLH etiological clusters

Patients, n(%)	**SEPSIS-HLH** **n = 121(47)**	**INTRACELLULAR INFECTION-HLH** **n = 84(32)**	**MALIGNANCY-HLH** **n = 28(11)**	**IDIOPATHIC HLH** **n = 27(10)**	**P**
IMMUNOSUPPRESSION, n(%)	81 (67)	42 (50)	27 (97)	15 (56)	< 0.001
None, n	40	42	1	11	-
SOT or HSCT, n	14	10	4	3	-
Ongoing solid cancer, n	29	12	6	5	-
Malignant hemopathy, n	33	12	22	6	-
Recent chemotherapy, n	40	14	8	6	-
HIV or AIDS, n	1	3	1	0	-
Other IS therapies, n	15	8	1	5	-
SEVERITY ASSESSMENT					
SOFA at ICU admission	9 [7–12]	8 [6–11]	8 [6–10]	9 [6–12]	0.04
Delta SOFA	3 [1–4]	4 [1–6]	3 [0–5]	3 [0–5]	0.15
HLH BIOLOGY	-	-	-	-	-
Hemoglobin, g/dL	8.2 [7.6-9]	8.5 [7.7-9]	7.9 [7.5–8.7]	8.4 [7.6–8.8]	0.49
Leukocytes, G/L	6.4 [2.9–14.2]	7.3 [3–18]	4.5 [2.2–7.8]	5.4 [3-11.8]	0.34
Neutrophils, G/L	5.2 [1.6–11.7]	6.5 [2.3–14.6]	3 [1.3–6.4]	5 [2-9.9]	0.39
Lymphocytes, G/L	0.4 [0.1–0.7]	0.5 [0.2–0.8]	0.4 [0.2–0.8]	0.5 [0.1–0.8]	0.87
Platelets, G/L	26 [13–52]	42 [18–68]	32 [11–49]	40 [18–56]	0.03
Fibrinogen, g/L	4.4 [3.3–6.4]	4.1 [2.3–6.1]	2.4 [1.8–5.2]	3.1 [2.1–4.6]	0.001
Ferritin, µg/L	2518 [1269–4271]	2837 [1360–5676]	5127 [3029–6841]	2325 [997–3859]	0.14

Patients, n(%)	SEPSIS-HLH n = 121(47)	INTRACELLULAR INFECTION-HLH n = 84(32)	MALIGNANCY-HLH n = 28(11)	IDIOPATHIC HLH n = 27(10)	P
ASAT, UI/L	62 [36–127]	85 [38–139]	74 [45–210]	51 [38–175]	0.37
ALAT, UI/L	59 [30–111]	51 [34–122]	47 [26–72]	5 [24–221]	0.56
Triglycerides, g/L	2.5 [1.7–3.6]	3 [1.9–4.1]	3 [2-4.3]	2.5 [1.1–4.3]	0.54
LDH, UI/L	461 [289–803]	491 [335–1012]	704 [304–1136]	843 [346–1661]	0.37
HLH DIAGNOSTIC CRITERIA					
Bone marrow HmP, n(%)	114(94)	77(92)	23(82)	23(85)	0.34
HScore	199 [175–219]	196 [177–228]	239 [213–270]	190 [171–221]	0.051
HLH probability with HScore, %	88 [64–96]	85 [67–98]	99 [94–100]	80 [55–97]	0.051
HLH-2004 criteria	4 [4–5]	5 [4–5]	5 [4–5]	4 [4–5]	0.79
HLH TREATMENT	-	-	-	-	-
Steroids, n(%)	51(42)	51(61)	19 (68)	20(74)	0.002
Ciclosporin A, n(%)	8(7)	3(4)	0(0)	4(15)	0.07
IV immunoglobulin, n(%)	4(3)	8(10)	3(11)	2(7)	0.23
Etoposide, n(%)	6(5)	8(10)	5(18)	2(7)	0.13
OUTCOMES					
ICU length of stay, days	23 [14–42]	28 [17–50]	14 [8–28]	24 [10–40]	0,08
ICU mortality, n(%)	64 (53)	51 (62)	17 (61)	15 (56)	0.59
6-month survival, n(%)	36 (30)	24 (29)	5 (18)	7 (26)	0.53

The clinical and biological differences between patients according to their binary ICU outcome (alive or deceased) are highlighted in Table 3. Deceased patients were older (65 years [55–71] versus 55 years [44–64], $p < 0.001$). The mortality rate for patients receiving renal replacement therapy also tended to be

higher (18% versus 10%, p = 0.07). Death correlated with a higher SOFA score at ICU admission (9 [7–12] versus 8 [7–11], p < 0.001) and a higher delta SOFA (4 [2–6] versus 2 [0–4], p < 0.001). Laboratory abnormalities associated with ICU mortality included lower hemoglobin values (8.2 g/dL [7.6–8.8] versus 8.4 g/dL [7.7–9.5], p = 0.01), higher LDH levels (545 UI/L [336–1012] versus 471 UI/L [294–917], p = 0.03) and more pronounced hepatitis (ASAT = 76 UI/L [37–214] versus 57 [36–132], p = 0.03; bilirubinemia = 46 µmol/L [21–118] versus 34 [16–66], p = 0.002). No significant differences were noted for platelet or leukocyte counts or fibrinogen, triglyceride, or ferritin levels between these two groups. A higher number of deceased patients received steroids (n = 88/147 (60%) versus 52/111 (47%), p = 0.04), whereas etoposide was equally administered between the groups. Multivariate analysis (Table 4) identified six mortality risk factors in ICU adult-acquired HLH: older age (OR (5 years) = 1.31 [1.16–1.48], p < 0.0001), higher SOFA score at ICU admission (OR = 1.37 [1.21–1.56], p < 0.0001), SOFA score aggravation between ICU arrival and HLH diagnosis (delta SOFA) (OR = 1.47 [1.28–1.70], p < 0.0001), presence of bone-marrow hemophagocytosis (OR = 5.27 [1.11–24.97], p = 0.04), and more severe anemia (OR = 1.44 [1.09–1.91], p = 0.01) and hypofibrinogenemia (OR = 1.21 [1.04–1.41], p = 0.02). HLH etiology was not an independent risk factor of ICU mortality.

Table 3
Differences between HLH patients according ICU mortality- univariate analysis

Patients, n(%)	**ALIVE** **n = 111(43)**	**DECEASED** **n = 147(57)**	**p**
AGE (years)	55 [44–64]	65 [55–71]	< 0.001
GENDER (M/F)	1.64/1	2.87/1	0.04
PRIOR IMMUNOSUPPRESSION, n(%)			
SEVERITY ASSESSMENT			
Invasive MV, n(%)	54(49)	84(57)	0.18
RRT, n(%)	11(10)	26(18)	0.08
SOFA at ICU admission	8 [7–11]	9 [7–12]	< 0.001
Delta SOFA	2 [0–4]	4 [2–6]	< 0.001
HLH BIOLOGY			
Hemoglobin, g/dL	8.4 [7.7–9.5]	8.2 [7.6–8.8]	0.01
Leukocytes, G/L	5 [1.9–13]	7.2 [3.1–14.6]	0.46
Platelets, G/L	35 [15–62]	33 [14–52]	0.62
Fibrinogen, g/L	4.4 [2.5–6.4]	3.9 [2.3–5.6]	0.051
Bilirubin, µmol/L	34 [16–66]	46 [21–118]	0.002
ASAT, UI/L	57 [36–132]	76 [37–214]	0.03
ALAT, UI/L	49 [28–104]	57 [32–135]	0.34
LDH, UI/L	471 [294–917]	545 [336–1012]	0.03
Ferritin, µg/L	2704 [1254–5191]	2681 [1325–5201]	0.20
Triglycerides, g/L	3 [1.9–4.2]	2.5 [1.7–3.8]	0.09
HLH criteria			
Bone marrow HmP, n(%)	95(91)	140(98)	0.01
HScore	200(88)	195(85)	0.867
HLH-2004 criteria	4[4–5]	5[4–5]	0.344
HLH therapies			
Steroids, n(%)	52 (47)	88 (60)	0.04
Etoposide, n(%)	6 (5)	15 (10)	0.16

Table 4
Multivariable analysis: mortality risk factors in ICU acquired adult HLH- logistic regression

Risk factors	Unit	OR [IC95%]	p
HLH etiology (ref = sepsis)			0,54
Others vs sepsis		1.72 [0.82–3.57]	0.1499
Cancer vs sepsis		1.39 [0.46–4.17]	0.5569
Idiopathic vs sepsis		1.43 [0.46–4.39]	0.537
Age	*+ 5 years*	1.31 [1.16–1.48]	< 0,0001
SOFA at ICU admission	*+ 1 point*	1.37 [1.21–1.56]	< 0,0001
Delta SOFA	*+ 1 point*	1.47 [1.28–1.70]	< 0,0001
Bone marrow hemophagocytosis	*Positive Vs Negative*	5.27 [1.11–24.97]	0.04
Hemoglobin	*− 1 point (g/dL)*	1.44 [1.09–1.91]	0.01
Fibrinogen	*− 1 point (g/L)*	1.21 [1.04–1.41]	0.02

Discussion

We report on one of the largest cohorts of ICU-acquired adult HLH [25]. Our retrospective findings need to be confirmed by further studies, as the number of HLH diagnoses could have been underestimated (potentially incomplete medical coding) or overestimated (low specificity of HLH-2004 and HScore criteria). In addition, retrospective etiological diagnosis can be difficult, as various concomitant etiologies can lead to HLH. Our reported cases are representative of the ICU population and are in accordance with the literature. We confirmed the association between acquired HLH and a poor prognosis, frequent multiorgan failure, and a propensity for a background of immunosuppression. The high ICU mortality rate varied from 50 to 60%, in accordance with both the adult and pediatric literature [25,26]. Mortality risk factors included age and the severity of organ failure assessed by the SOFA score [27-29]. The worsening of organ failure prior to the HLH diagnosis led to a worse prognosis (Delta SOFA). The Delta SOFA slightly correlated with a longer time interval between ICU admission and HLH diagnosis (Rho = 0.19, p = 0.002). This finding underscores the necessity of a prompt diagnosis and immediate treatment, although ICU-acquired HLH is still widely underdiagnosed according to the literature [30]. Persistent fever that is refractory to antibiotics, pancytopenia, major hyperferritinemia, or unexplained chemical hepatitis should lead practitioners to screen patients for HLH [31-33]. Although variable and non-specific, bone-marrow hemophagocytosis is still a hallmark HLH criterion [34-36] and was associated with a higher ICU mortality rate in our study. Among biological factors, non regenerative profound anemia and hypofibrinogenemia have been reported to be independent predictors of a poor outcome [27-29,37]. The severity of cytopenia and coagulopathy have been shown to correlate with both the prognosis and TNF-a and IFN-g-mediated cytokine storm flares [2,3]. High ferritin levels were not significantly associated with ICU mortality,

contrary to the literature [27,33]. Ferritinemia is a reflection of macrophage activation and the IL-1b/IL-18 signaling pathway and is a reliable HLH biomarker for disease follow-up and monitoring, although the 500 µg/L threshold currently used has been shown to have poor sensitivity and specificity in the ICU [38-42].

In our study, mortality was not significantly associated with HLH etiology. However, reported mortality was higher for patients with underlying lymphoma or intracellular infection (60%) than for those idiopathic or sepsis-related HLH (50-55%). None of our patients presented with iatrogenic HLH following the administration of CAR T-cells or other immunotherapy [43]. Aggressive lymphoma further worsened the poor outcome due to the exacerbation of organ failure [44,45]. Patients admitted to the ICU with intracellular infections (mycobacteria, pneumocystosis, *Herpesviridae*) tended to have a greater mortality rate due to underlying severe comorbidities and/or immunosuppression.

We expected the prognosis to differ according to HLH physiopathology. Lymphocytes can initiate HLH and cytokine storms (lymphoid HLH). The pathophysiology of EBV-associated HLH implies an immune defect that leads to lymphoproliferation [46,47]. The involvement and proliferation of a tumor clone was evident in the pathogenesis of lymphoma-associated HLH. However, lymphoproliferation was not encountered in sepsis-associated HLH. Such patients show enhanced lymphopenia and tissue lymphocyte apoptosis [48,49]. Hence, sepsis-associated HLH would imply a myeloid-induced cytokine storm (myeloid cell-associated HLH). *Toll Like Receptors* have been shown to sustain stimulation in murine models and human inflammasome gain-of-function genetic mutations have been associated with HLH [50-55]. Myeloid versus lymphoid onset thus illustrates two separate pathophysiological mechanisms, highlighting the necessity of better-targeted therapies. Anti-lymphoproliferative treatments, such as etoposide and ciclosporin A, would solely be of interest in lymphoma or EBV-associated HLH, alone or associated with an etiological treatment (rituximab for EBV, specific chemotherapy for lymphoma). These therapies should not be used in sepsis-related HLH. The most severe and hyperinflammatory cases of sepsis-associated HLH could benefit from therapies that target cytokine storms, such as anakinra (anti-IL-1), tocilizumab (anti-IL-6), and/or ruxolitinib (anti-JAK2) [16,56,57].

Our study did not reveal any differences in the prognosis according to the specific administered HLH treatment. However, the number of treated patients, especially those treated with ciclosporin A, etoposide, and intravenous immunoglobulin (IVIG), was too low to show any statistical pattern. As IVIG administration is safer than HLH immunosuppressive therapies, its use in non-malignancy-related HLH needs to be studied in a prospective-controlled trial [58]. Based on the literature, patients with malignancy-associated HLH and EBV-associated HLH should receive early targeted therapy [29,59]. For other HLH etiologies, the use of steroids has been debated but does not appear to provide any benefit [60]. The recently approved anti-IFN-gamma monoclonal antibody (emapalumab) is strictly applicable to only primary HLH and cannot be extended to ICU-acquired HLH [61].

Conclusion

Still underdiagnosed, hemophagocytic lymphohistiocytosis was associated with a 50 to 60% mortality rate in the ICU, reaching 70% at the six-month follow-up. The prognosis worsens with the severity of organ failure and cytokine storms. An often non-specific clinical and/or biological set of arguments, above all for immunosuppressed patients, should lead practitioners to search for HLH. Thorough and rapid etiological screening is an absolute priority as it leads to rapid selection of appropriate targeted therapy. Patients with HLH due to lymphoproliferative triggers would likely benefit from anti-lymphocyte proliferation treatment (etoposide), whereas myeloid cell-associated HLH, such as that encountered in sepsis, should probably be treated with anti-cytokine storm therapies on a case-by-case basis. Clinical trials must be developed to confirm these hypotheses.

Declarations

Ethical Approval and Consent to participate

This retrospective study was communicated to the Commission on Data Processing and Freedom representative of each center and approved by APHM ethic committee (#2019-316).

Consent for publication

Written informed consent was not obtained for publication of these data. Consent to publish was not applicable for this study.

Availability of supporting data

All data can be requested from Dr Amandine BICHON, email Amandine.BICHON@ap-hm.fr

Competing interests

The authors declare that they have no competing interests.

Funding

The authors declare that they received no funding.

Authors' contributions

JC devised and supervised the study. AB and JC performed research. AB and JC wrote the manuscript. AB is the guarantor for the content of the manuscript, including the data and analysis. VP analyzed the data. AB, JB, JAS, LP, SH, CG, DM, MG and JC took care of patients. GK provided key expertise. All authors read and approved the final manuscript.

Acknowledgements

None.

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