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Coagulation Disorders and Bleedings in Critically Ill Patients With Hemophagocytic Lymphohistiocytosis

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Abstract: Reactive hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition related to a cytokine storm leading to multiorgan dysfunction. A better understanding of coagulation disorders, frequently reported in HLH patients, may improve outcomes.

Critically ill HLH patients managed in a multidisciplinary national reference center were retrospectively included. Relationships between coagulation disorders, severe bleedings, and outcomes were assessed.

One hundred and seventeen patients fulfilled the HLH 2004 criteria. The most common HLH etiology was hematologic conditions (73%), followed by infectious diseases (20%), systemic rheumatic diseases (5%), and undetermined HLH etiology (3%). All patients exerted thrombocytopenia. Coagulation disorders were diagnosed in 79 (68%) patients (61 had hypofibrinogenemia < 1.5 g/L, 51 had prothrombin time [PT] < 50%). The worst median value throughout ICU stay was 52% (38–65) for PT with a factor V level of 35% (27–43), 1.59 (1.30–2.09) for the activated partial thromboplastin time (APTT) ratio, and 2.33 g/L (1.13–3.86) for the fibrinogen level. Disseminated intravascular coagulation (DIC) was found in 50% of patients. Coagulation disorders were more frequent in immunocompromised patients, those with histological/cytological feature of hemophagocytosis, those with the highest ferritin concentrations, and in patients with HLH not related to infection. These patients were more prone to receive mechanical ventilation, vasopressors, or renal replacement therapy. Twenty-six (22%) patients presented severe bleeding complications, including 5 patients dying from hemorrhagic shock. Strikingly, the only coagulation parameter significantly associated with severe bleeding was low fibrinogen with a cutoff value of 2 g/L ($P = 0.03$). Overall, 33 (28%) patients died in the ICU and hospital mortality was 44%. Coagulation disorders were associated with higher mortality, especially fibrinogen < 2 g/L ($P = 0.04$) and PT value ($P = 0.03$). The occurrence of bleeding complications was not associated with higher risk of hospital death. Risk factors associated with mortality by multivariate analysis were fibrinogen level < 2 g/L (OR 2.42 [1.08–5.41]), SOFA score > 6 (OR 3.04 [1.32–6.98]), and age > 46 years (OR 2.26 [1.02–5.04]).

Up to two-third of critically ill HLH patients present with coagulation disorders. Hypofibrinogenemia or DIC was found in half of the patients and low PT in 40%. These patients require more life support and have a higher mortality rate. Fibrinogen <2 g/L is associated with the occurrence of severe bleeding and mortality.

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Abbreviations: APTT = activated partial thromboplastin time, DIC = disseminated intravascular coagulation, EBV = epstein barr virus, HLH = hemophagocytic lymphohistiocytosis, ICU = intensive care unit, IL = interleukin, IQR = interquartile range, PT = prothrombin time, SOFA = sepsis-related organ failure assessment, TNF = tumor necrosis factor.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a cytokine storm syndrome characterized by overactivation of cytotoxic T cells with hemophagocytosis by macrophages. In adults, reactive HLH mainly occurs as a complication of immune deficiencies. Triggers of HLH chiefly include infections, hematologic neoplasms, solid malignancies, and autoimmune diseases.[1–3]

Hemophagocytic lymphohistiocytosis is a rare condition whose diagnosis relies on the HLH 2004 criteria issued by the Histiocyte Society (Table 1).[4] In the most severe cases, the cytokine storm can cause multiorgan failure with involvement of the neurologic, cardiovascular, hepatic, and/or respiratory system. Mortality rate varies with the underlying disease and triggering condition and may reach 70%.[3,5,6] Early administration of etoposide has been associated with a better outcome in EBV (Epstein–Barr virus)-associated HLH.[7]

Coagulation disorders are common in HLH patients, being described in more than half of the cases.[1,8,9] Adverse outcomes have been reported due to both bleeding complications and inability to optimally manage HLH patients.[10–12] The most frequently reported hemostasis abnormality consist in an isolated decrease of the fibrinogen level. The mechanisms of this hypofibrinogenemia are incompletely understood and putatively ascribed to hyperfibrinolysis.[1,9,13] Alternatively, hypofibrinogenemia may be related to fibrinogen consumption by disseminated intravascular coagulation (DIC), also described in severe HLH cases.[3,9] Less frequently, a decreased fibrinogen production in the context of macrophage infiltration of the liver or by the cytokine storm has also been described.[14] Studies have shown that DIC and thrombocytopenia were associated with adverse outcome in HLH patients.[5,9,15,16]

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TABLE 1. Revised Diagnostic Guidelines for HLH[4]

The diagnosis HLH can be established if 1 of either 1 or 2 below is fulfilled:
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting $\geq$ 2 of 3 lineages in the peripheral blood)
Hemoglobin $<$ 90 g/L (in infants $<$ 4 weeks: hemoglobin $<$ 100 g/L)
Platelets $< 100 \times 10^9$/L
Neutrophils $< 1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides $\geq$ 3.0 mmol/L (ie, $\geq$ 265 mg/dL)
Fibrinogen $\leq$ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin $\geq$ 500 mg/L
Soluble CD25 (ie, soluble IL-2 receptor) $\geq$ 2400 U/mL

HLH = hemophagocytic lymphohistiocytosis, NK = natural killer.

TABLE 2. Algorithm for the Diagnosis of Overt Disseminated Intravascular Coagulation[17]

(1) Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?
If yes proceed, if no do not use this algorithm
(2) Order global coagulation tests (platelet count, prothrombin time, fibrinogen, soluble fibrin monomers, or fibrin degradation products)
(3) Score global coagulation test results
a. Platelet count ($>$ 100 = 0, $<$ 100 = 1, $<$ 50 = 2)
b. Elevated fibrin-related marker (no increase = 0, moderate increase = 2, strong increase = 3)
c. Prolonged prothrombin time ($<$3 s = 0, $>$3 s but $<$ 6 s = 1, $>$6 s = 2)
d. Fibrinogen level ($>$1 g/L = 0, $<$1 g/L = 1)
(4) Calculate score
(5) If $\geq$ 5: compatible with overt DIC; repeat score daily
If $<$ 5: suggestive (not affirmative) for nonovert DIC; repeat next 1–2 days

DIC = disseminated intravascular coagulation.

Our objectives here were to describe coagulation disorders in critically ill patients with HLH and to determine whether coagulation abnormalities and bleedings influenced outcomes.

Patients and Methods

Our institutional review board approved the study and waived the need for informed consent in accordance with French legislation on retrospective studies. We retrospectively reviewed the medical charts of consecutive adult patients admitted to the intensive care unit (ICU) of a university hospital from January 1, 2007 to December 31, 2014, with a diagnosis of HLH.

Hemophagocytic lymphohistiocytosis diagnosis was established by fulfilling 5 of the 8 criteria developed by the Histiocyte Society in 2004 (Table 1).[4] Disseminated intravascular coagulation was defined according to the score of the International Society on Thrombosis and Haemostasis (Table 2).[17] Hemophagocytosis was defined as histological evidence of activated macrophages engulfing erythrocytes, platelets, and/or nucleated cells or their precursors, in bone marrow smear and/or biopsy of bone marrow, liver, spleen, or lymph node.

All patients were managed jointly by hematologists/immunologists belonging to the clinical immunology ward and ICU teams. Data reported in tables and figures were abstracted from the medical records. We recorded the treatments used for the HLH and for its etiology. Coagulation disorders were defined by a PT (prothrombin time) $<$50% and/or a fibrinogen $<$2 g/L and/or elevated fibrin degradation products. Serious bleeding complication was defined by the need for any red blood cells transfusion, hemostatic surgery, or embolization. At admission, all patients have been tested for the most common bleeding disorders using the standard both hemostatic inquiry and laboratory testing. None of them were identified to have either an inherited bleeding disorder (ie von Willebrand disease for example) or an acquired auto-immune bleeding disorder (ie acquired hemophilia A for example) that could have majored their bleeding symptoms. Intensive care unit and hospital mortality were available for all studied patients.

Statistical Analysis

Quantitative parameters were described as median (interquartile range [IQR]) and qualitative parameters as number (%). Categorical variables were compared using Fisher's exact tests and continuous variables using Wilcoxon rank-sum tests. Our primary endpoint was hospital mortality. The second outcome variable of interest was significant clinical bleedings as defined by the need for any red blood cells transfusion.

To identify associations between patients' characteristics (including clinical bleedings and coagulation disorders) and hospital mortality, we performed a logistic regression model. Factors included in the multivariate regression model were selected for their clinical relevance among variables yielding P values $<$0.20 in the univariate analysis. No hypotheses were made for missing variables that were left in blank and not introduced in the logistic regression model. The final multivariate model was selected by a backward stepwise procedure based on the P value.

All tests were 2-sided and P values $<$ 0.05 were considered as indicating significant association. All statistical analyses were carried out using a personal computer with StatView version 4.0 (SAS Institute, Inc, Berkeley, CA).

RESULTS

We identified 117 patients with HLH (34 women and 83 men, median age of 46 years [IQR, 37–57]) admitted to our ICU over the study period. Main reasons for ICU admission included acute respiratory failure (n = 28, 24%), shock (n = 23, 20%), acute kidney injury (n = 14, 12%), and coma (n = 9, 8%). In line with HLH 2004 criteria, fever was present in 96% of cases

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(n = 112), hepatosplenomegaly in 79% of cases (n = 92), and bi or pancytopenia in 67% (n = 78). All patients had hyperferritinemia >500 μg/L (median value of ferritin was 7897 ng/mL [4351–25 050]). Sixty-one (52%) patients presented with hypofibrinogenemia <=1.5 g/L and/or hypertriglyceridemia >=3 mmol/L. Features of hemophagocytosis were identified in 91 (78%) patients.

Hemophagocytic lymphohistiocytosis was diagnosed 10 days [2–17] before ICU admission in 50 patients (43%) and at ICU admission in 67 (57%). The most common HLH-triggers were hematologic conditions (hematologic malignancies and HHV8-related diseases) in 85 patients (73%), infectious diseases in 23 (20%), and systemic rheumatic diseases (adult onset Still's disease in half of the cases) in 6 (5.1%). Despite an extensive etiologic workup, HLH etiology remained unidentified in 3 patients.

All patients exerted thrombocytopenia. Coagulation disorders were diagnosed at ICU admission in 70 (60%) patients and throughout the ICU stay in 79 (68%) patients. Disseminated intravascular coagulation was found in 50% of patients. The worst coagulation parameter values throughout the ICU stay were 18 000/mm^3 (8500–41 000) for platelet count, 52% (38–65) for PT, 1.59 for the APTT (activated partial thromboplastin time) ratio (1.30–2.09), and 2.33 g/L (1.13–3.86) for the fibrinogen level. Forty-eight patients (41%) had a PT <50% throughout the ICU stay with a factor V level of 35% (27–43). As shown in Table 3, more patients with coagulation disorders were previously known as immunocompromised or had features of hemophagocytosis. Patients with infectious-related HLH presented less frequently with coagulation disorders. Last, ferritin concentrations at admission were higher in patients with coagulation disorders. Table 4 discloses that patients with coagulation disorders required more life support than other patients.

Twenty-six (22%) patients presented severe bleeding complications on admission or throughout the ICU stay, including 5 patients for whom bleeding complications were the primary reason for death. Underlying malignancies were not associated with an increased occurrence of serious bleeding complications. Strikingly, the only coagulation parameter that was significantly associated with severe bleeding by univariate analysis was low fibrinogen rate with a cutoff value of 2 g/L ($P = 0.03$). Overall, 33 (28%) patients died in the ICU and hospital mortality was 44%. Coagulation disorders were associated with

TABLE 3. Patients and HLH Characteristics at ICU Admission

N (%) or Median (IQR)	Coagulation Disorders (N = 79)	No Coagulation Disorders (N = 38)	*P* Value
Demographics			
Age	46 [37–59]	45 [35–54]	0.20
Female gender	23 (29%)	11 (29%)	0.98
Previously known immunosuppression	43 (54%)	29 (76%)	<0.001
HIV infection	30	14	
Other	13	15	
HLH characteristics at admission			
Time (days) from diagnosis to ICU admission	0 [0–7]	0 [0–7]	0.79
Presence of fever (>38.5 °C)	76 (96%)	36 (95%)	0.71
Spleen and/or liver enlargement	63 (80%)	26 (68%)	0.15
Ferritin concentration (μg/L)	10659 [5350–40449]	6067 [4011–9474]	0.007
Triglycerides concentration (g/L)	2.68 [2.08–4.24]	3.09 [2.37–3.7]	0.37
Feature of hemophagocytosis	65 (82%)	21 (55%)	0.001
HLH trigger			0.02
Hematologic conditions	62 (78%)	23 (60%)	
T cell lymphoma	19 (31%)	6 (26%)	
Castleman disease/Kaposi sarcoma	14 (22%)	10 (43%)	
B cell lymphoma	16 (26%)	3 (13%)	
Hodgkin lymphoma	9 (14%)	1 (4%)	
Other lymphoma	3 (5%)	1 (4%)	
Other hematologic malignancy	1 (2%)	2 (9%)	
Infectious diseases	10 (13%)	13 (34%)	
Mycobacterium infections	5 (50%)	4 (31%)	
Fungi/parasites	4 (40%)	4 (31%)	
Viruses	0	5 (38%)	
Other bacteria	1 (10%)	0	
Systemic diseases	4 (5%)	2 (5%)	
Adult onset Still's disease	3 (75%)	0	
Other	1 (25%)	2 (100%)	
Undetermined HLH etiology	3 (4%)	0	
SOFA score at admission	8 [6–11]	6 [4–8]	0.001

HLH = hemophagocytic lymphohistiocytosis, ICU = intensive care unit, IQR = interquartile range, SOFA = sepsis-related organ failure assessment.

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TABLE 4. Coagulation Disorders, Bleedings, and Outcomes

N (%) or Median (IQR)	Coagulation Disorders (N = 79)	No Coagulation Disorders (N = 38)	*P* Value
Hemostasis data			
Platelets count (G/L)	15 [7–30.75]	32 [12–68]	0.001
Prothrombin time (%)	46 [34–54]	69 [63–75]	<0.001
APTT ratio	1.72 [1.46–2.2]	1.37 [1.14–1.59]	<0.001
Fibrinogen (g/L)	1.5 [0.86–3.21]	3.75 [2.6–4.9]	<0.001
Bleeding complications	21 (26%)	5 (13%)	0.10
Time (days) since ICU admission	0.5 [0–4]	0 [0–1.5]	0.92
Time (days) since HLH diagnosis	3.5 [0.5–14.5]	3 [0–21]	0.84
Bleeding Sites			0.03
Intracranial	3 (14%)	2 (40%)	
Gastrointestinal/ENT	13 (62%)	1 (20%)	
Skin hematoma/vascular access	2 (10%)	0	
Pulmonary	3 (14%)	2 (40%)	
Bleeding after invasive procedures*	5 (24%)	2 (40%)	0.50
Thrombotic complications	1 (1.2%)	2 (5%)	0.58
Treatments in the ICU			
Mechanical ventilation	48 (61%)	15 (39%)	0.03
Vasopressors	43 (54%)	8 (21%)	0.0007
Renal replacement therapy	36 (46%)	9 (24%)	0.02
HLH-related therapies			
Etoposide	66 (84%)	24 (63%)	0.009
Dose (mg)	200 [200–200]	200 [157.5–200]	0.29
Time (days) since ICU admission	0 [0–1]	0 [0–0.5]	0.92
Corticosteroids	62 (78%)	16 (42%)	0.0002
Intravenous immunoglobulins	6 (7%)	6 (16%)	0.17
Outcomes			
Length of ICU stay (days)	6 [3–11]	4 [2–8]	0.008
ICU deaths	26 (33%)	7 (18%)	0.10
Hospital deaths	38 (48%)	13 (34%)	0.16

HLH = hemophagocytic lymphohistiocytosis, ICU = intensive care unit, IQR = interquartile range, ENT = ear nose throat.
* Invasive procedures were transcutaneous lymph node biopsy, n = 2, transparietal liver biopsy, n = 1, transjugular liver biopsy, n = 1, surgery (splenectomy), n = 1, transthoracic lung biopsy, n = 1, rectal biopsy, n = 1.

higher mortality, especially fibrinogen <2 g/L ($P = 0.04$) and worst PT ($P = 0.03$). Hospital mortality according to the presence and extent of coagulation disorders is illustrated in Figure 1. The occurrence of bleeding complications was not associated with higher risk of hospital death. By multivariate analysis, factors associated with hospital mortality were fibrinogen level <2 g/L, age >46 years, and SOFA (sepsis-related organ failure assessment) score at ICU admission >6. Overall survival according to the fibrinogen level, prothrombin time, and SOFA score is represented in Figure 2.

DISCUSSION

To the best of our knowledge, this is the largest study assessing coagulation disorders in severe HLH patients admitted to the ICU. Coagulation disorders are common in HLH patients[1,8,9] and increase significantly the risk for bleeding and hospital mortality.

Hypofibrinogenemia <2 g/L is independently associated with increased mortality in our study. This is in line with a previous study that reported adverse impact of fibrinogen level with a threshold < 1.6 g/L in HLH patients. The mechanisms leading to hypofibrinogenemia are probably complex and not yet fully understood. The very low fibrinogen level may reflect

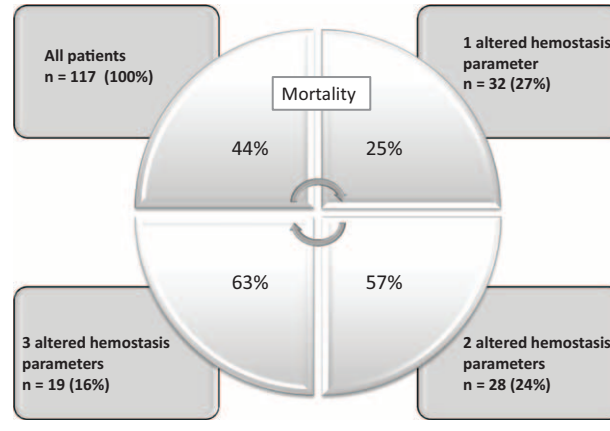

FIGURE 1. Hospital mortality according to the presence and extent of coagulation disorders. Altered hemostasis parameters included PT <50%, fibrinogen <2 g/L, and elevated fibrin degradation products. Thirty-eight (32%) patients did not present any coagulation disorder. PT = prothrombin time.

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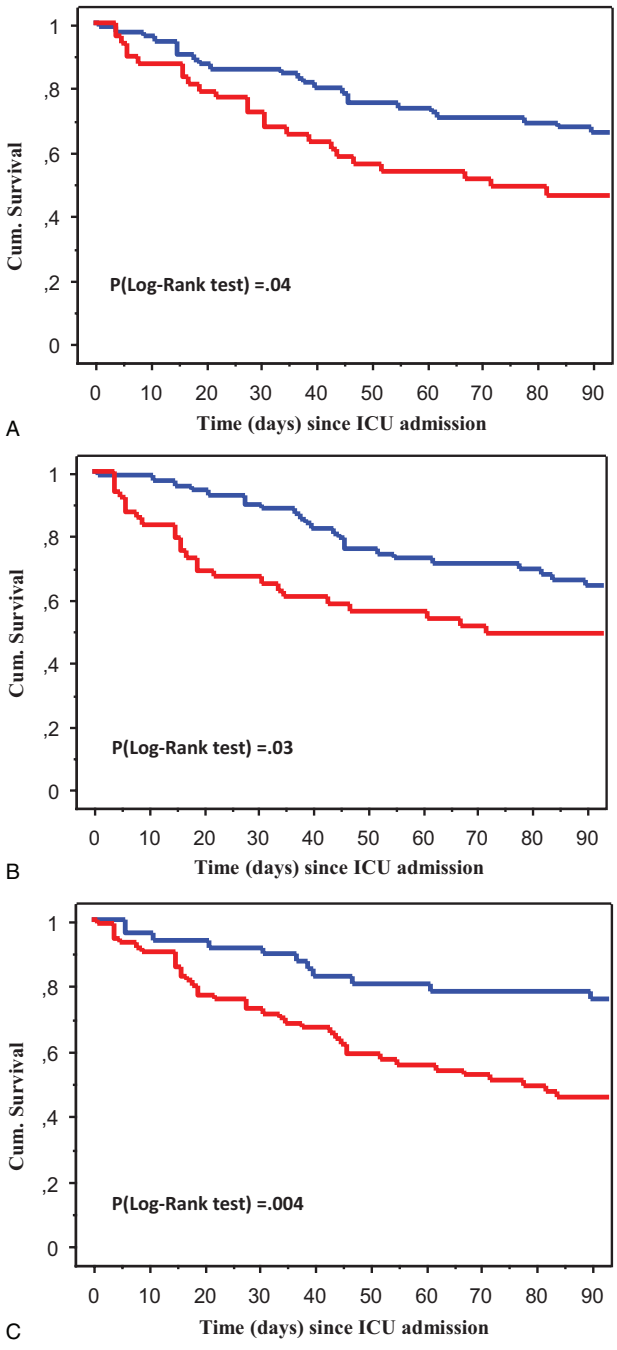

FIGURE 2. Survival as a function of fibrinogen level, PT and SOFA score. 2A: red line represents the fibrinogen level <2 g/L and blue line the fibrinogen level ≥ 2 g/L. 2B: red line represents PT <50% and blue line PT ≥ 50%. 2C: red line represents the SOFA score > 6 and blue line the SOFA score ≤ 6. PT = prothrombin time, SOFA = sepsis-related organ failure assessment.

not only a process of DIC,[3,9] consisting in secondary fibrinolysis, but also a process of primary hyperfibrinogenolysis. One hypothesis is that fibrinogen degradation is linked to the secretion of plasminogen by activated macrophages in response to the production of IL-1 beta (Interleukin 1) and TNF (tumor necrosis factor) by activated lymphocytes.[3,18,19] This latter mechanism is potentially similar to the hyperfibrinogenolysis commonly observed in prostatic or uterine carcinoma for example and, in contrast to DIC, this mechanism usually does not induce a major thrombocytopenia. The fact that the low fibrinogen level is associated with mortality in our study may suggest a specific prognostic role for primary hyperfibrinogenolysis in severe HLH. Furthermore, fibrinolysis may also be triggered by an increased expression of tissue factor by monocytes and macrophages.

Coagulation disorders were more common in patients with hematologic conditions-related HLH in comparison to patients with an infectious-related HLH. This could be explained in part by potential hepatic infiltration by lymphoma cells in this group of patients. Moreover, DIC and primary fibrinolysis are not infrequent in patients with hematologic malignancies.[20,21] In addition, coagulation disorders have been reported in patients treated for hematologic malignancies with impaired hemostasis functions leading to a higher risk of bleeding.[22] Whether the high prevalence of coagulation disorders in this study is related to the large number of patients with lymphoma remains unanswered.

Interestingly, this study assessed both coagulation disorders and bleedings. However, bleedings were not associated with mortality whereas coagulation disorders did. We were not able to adjust on transfusion protocols and HLH treatments. In our study, only 5 deaths were directly linked to a bleeding complication. This emphasizes the hypothesis that coagulation disorders may reflect HLH severity resulting in multiorgan failure. Indeed patients with coagulation disorders had a greater hemophagocytic activity with higher ferritin levels and more common cytological hemophagocytosis on bone marrow examination. These patients were also more critically ill with a higher SOFA score and required more life-sustaining therapies (mechanical ventilation, vasopressors, and dialysis). Patients with coagulation disorders received more frequently specific treatments for HLH (etoposide and corticosteroids) because of their clinical and biological extreme severity at admission.

This study had several limitations, due to its retrospective and single-center design. Furthermore, there was a recruitment bias since a majority of hematological patients was admitted to our ICU. Our data therefore may not be generalized to the entire population of patients with HLH in ICU. We were not able to collect data on transfusion requirements, which may have influenced the platelet counts, fibrinogen and PT levels. However, we believe that these results provide an awareness of the importance of coagulation disorders in HLH patients, stressing out the need to further investigate these issues.

In conclusion, this preliminary study shows that coagulation disorders are common in ICU patients with severe HLH. Fibrinogen level <2 g/L and low PT were associated with higher mortality. Bleeding complications occurred in 22% of the patients and were only associated with hypofibrinogenemia <2 g/L. To improve the understanding of hemostasis disorders and the management of patients at high risk of morbidity and mortality in ICU, a prospective study evaluating the mechanisms of fibrinolysis and coagulation disorders in HLH patients is warranted.

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