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ORIGINAL ARTICLE

Biomarkers for Early Diagnosis of Hemophagocytic Lymphohistiocytosis in Critically Ill Patients

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Abstract

Many biomarkers have been proposed for the diagnosis of secondary hemophagocytic lymphohistiocytosis (HLH) in adults, but comparative studies are lacking. We analyzed ferritin, glycosylated ferritin, soluble CD25, CD163 and CD14, IL-6, IFN-γ, IL-18, IL-10, IL-1ß, IL-12p70, IL-17α, IP-10, and CXCL9 levels to differentiate HLH from sepsis in critically ill patients. Of 120 patients, HLH was confirmed for 14 patients. Among the biomarkers tested, ferritin, IL-18, and glycosylated ferritin were the most efficient parameters for early diagnosis of HLH. With a sensitivity set at 85%, ferritin, IL-18, and glycosylated ferritin were the biomarkers with the highest specificity: 84, 79, and 71% respectively. Combining IL-18 with the HScore provided a new score with an increased specificity compared to the HScore alone, 86% compared to 70% with a sensitivity set at 100%. A distinct cytokine pattern was highlighted in patients with malignancy-triggered HLH, with highly increased levels of INF-ɣ and CXCL9, compared to HLH secondary to infection. This is the largest study available to date, comparing diagnostic biomarkers for HLH on a cohort of critically ill adult patients. Serum ferritin was the most discriminating parameter for early diagnosis of secondary HLH. IL18*HScore was identified as a highly potential score.

Keywords Ferritin · hemophagocytic lymphohistiocytosis · hemophagocytic syndrome · HScore · interleukin-18

Introduction

Making an early diagnosis of a cytokine storm syndrome before progression to life threatening, multiple organ dysfunction remains a clinical challenge. Moreover, prompt institution of adequate treatment depends on the identification of the underlying triggers.

The cytokine storm syndrome encompasses familial and secondary hemophagocytic lymphohistiocytosis (HLH) as well as sepsis-associated macrophage activation-like syndrome. They correspond to a hyperinflammatory hyperferritinemic and dysregulated immune host response to different potential triggers like infections, malignancies, autoinflammatory, or autoimmune disorders and in some cases promoted by an immunodeficiency or an associated genetic disorder [1, 2]. In adults, infections and malignancies, mainly lymphomas, are the most prevalent triggers of HLH [3].

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HLH should be considered in any adult patient with unexplained fever, bicytopenia, and organ dysfunction. However, clinical presentations are broad and it may initially be difficult to distinguish HLH from symptoms of the underlying disease process. In the critical care setting, the clinical presentations of HLH and sepsis frequently overlap [4].

Besides the HLH-2004 criteria [5] and the HScore [6], different biomarkers have been proposed to help with the diagnosis of HLH. Marked hyperferritinemia (included in these diagnostic tools) should always prompt consideration of HLH in the differential diagnosis but is less specific in adults compared to children and is more frequently seen in renal or liver diseases, infections, and malignancies [7, 8]. A decreased percentage of glycosylated ferritin has been suggested to be a more specific marker to confirm the diagnosis of HLH [9, 10]. Recently, different studies have suggested that the pattern of inflammatory cytokines released may be useful to differentiate HLH from infection and other causes of hyperferritinemia [11–16] and also to distinguish the background disease process of the cytokine storm syndrome [17].

We therefore conducted a prospective observational study to evaluate the performances of the inflammatory markers, including ferritin, glycosylated ferritin, soluble CD25 (sCD25), soluble CD163 (sCD163) and soluble CD14 (sCD14), IL-6, IFN-γ, IL-18, IL-10, IL-1ß, IL-12p70, IL-17α, IP-10, and CXCL9, for the early diagnosis of HLH in an adult cohort of suspected cases compared to patients with sepsis admitted in the intensive care unit (ICU). We illustrated the relationship between the HScore and these biomarkers and analyzed the cytokines' pattern depending on the underlying disease in HLH patients.

Methods

Study Design

The study was conducted from July 2014 to February 2016 in four university-affiliated tertiary hospitals (one adult oncology center, Institut Jules Bordet, and three major university hospitals, Centre Hospitalier Universitaire Brugmann, Centre Hospitalier Universitaire Saint Pierre, and Hôpital Erasme–Cliniques Universitaires de Bruxelles) all in Brussels, Belgium. The study was approved by the ethics committees of each institution (2411, CE2014/33, AK/15-06-69/4524, P2014/336) and registered in ClinicalTrials.gov (NCT02143986).

The inclusion criteria were as follows: adult patients with a request for bone marrow aspiration in case of HLH suspicion, which is a routine hospital procedure in cases where patients present with signs and symptoms compatible with HLH, or the presence of sepsis (criteria described in [18]) at admission in ICU.

All enrolled patients were reclassified into different categories, namely, sepsis (according to [18]) or as having HLH based on the final diagnosis retained by the medical team caring for the patient. This diagnosis was based on the HLH-2004 diagnostic criteria amended to presume the diagnosis of HLH when at least four among six of the remaining criteria (including fever, splenomegaly, bicytopenia, hypertriglyceridemia, and/or hypofibrinogenemia, hyperferritinemia, and hemophagocytosis) were met. For doubtful cases, one of the authors (N.M.), who had at least 10 years' experience in diagnosis of and care for patients with HLH, reclassified the patients as positive or unconfirmed HLH based on their medical records (including evolution and response to treatment). The control groups finally consisted of patients for whom the diagnosis of HLH was not retained by the medical team and patients with sepsis.

Blood was sampled within the first 24 h of admission in the ICU for septic patients or concomitant with the bone marrow aspiration for the HLH suspected cases, so they correspond to an initial presentation data set. Serum samples were separated from the blood, divided into aliquots, and frozen and stored at -80 °C before analysis.

Data Collection and Laboratory Analyses

Further work-up included recording of relevant demographic and clinical information such as age, sex, highest recorded temperature, presence of hepatomegaly/splenomegaly, earlier medical history, known underlying immunosuppression (due to human immunodeficiency virus (HIV) or treatment with an immunosuppressive agent), treatment prescribed, and underlying disease. The following laboratory data were also collected concomitant to admission in ICU for septic patients or concomitant to the bone marrow aspiration for HLH suspected cases: hemoglobin levels; platelet, leukocyte, neutrophil, and lymphocyte counts; liver enzymes; ferritin; triglycerides; fibrinogen levels; and the presence or absence of images of hemophagocytosis on bone marrow smears. The HScore was determined for all the patients as described by Fardet et al. [6]. This score corresponds to a set of weighted criteria, including hemoglobin level, leucocyte and platelet counts, ferritin, triglycerides, and fibrinogen and ASAT levels, allowing effective estimation of the individual's risk of having HLH.

Serum concentration of ferritin was determined with the CENTAUR chemiluminescent immunoassay (Siemens Healthcare, Erlangen, Germany). The percentage of glycosylated ferritin was measured according to the method of Worwood et al. [19] with minor modifications. Serum concentration of sCD25,sCD163, and sCD14 were determined with the Quantikine ELISA Human CD25, CD163, and CD14 immunoassay, respectively (R&D Systems, Minneapolis, USA). Multiplex cytokine measurements (IL-

6, IFN-γ, IL-18, IL-10, IL-1ß, IL-12p70, IL-17α, IP-10, and CXCL9) on the serum were performed using a plate-based electrochemiluminescence assay according to the manufacturer's instructions (MSD, Meso Scale Discovery, Rockville, USA).

Statistical Analysis

Categorical variables were presented as an absolute number expressed in terms of percentage. To compare the diagnostic performances of the different inflammatory biomarkers to discriminate patients with HLH from control patients, we determined their diagnostic sensitivity and specificity using as reference the diagnosis retained by the medical team. The optimal cutoff value (with the highest Youden index) was obtained by receiver operating characteristic (ROC) curve analysis. ROC curve analysis also allowed determination of discrimination ability as measured by the area under the curve for each biomarker. A multivariate analysis by principal component analysis (PCA) was performed in order to corroborate the biomarker profile of HLH patients, using R [20] and FactoMine R [21]. Nonparametric Kruskal-Wallis test was used for the analysis of variance, followed by Dunn's multiple comparison test for the comparison of more than two groups. The nonparametric Spearman rank correlation coefficient (rs) was used for correlation analysis. p values were given as significant if $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ and nonsignificant (ns). Statistical analysis of data was performed using GraphPad Prism 5 (GraphPad Software, San Diego, CA) unless specified.

Results

Demographic Data

To compare the diagnostic sensitivity and specificity of serum biomarkers for the diagnosis of HLH in adults, serum inflammatory markers and cytokines levels were determined in 93 patients with sepsis and 27 patients with suspected HLH. Of these 120 patients, 14 samples were obtained at the time of initial presentation for HLH patients (concomitant with bone marrow aspiration). The control group consisted of 13 samples of unconfirmed HLH patients (concomitant with bone marrow aspiration) and 23, 37, and 33 samples of patients with septic shock, severe sepsis, and sepsis, respectively (obtained on ICU admission) (Fig. 1). Clinical characteristics of patients are shown in Table 1. All patients with a positive HScore (≥ 169 points) were in the HLH group; 3 HLH patients had a negative HScore at initial presentation. Infection (whether or not associated with hematologic malignancy) was the predominant cause of HLH (64%), followed by hematologic malignancy alone (29%).

Comparison of Serum Biomarkers for the Diagnosis of HLH

The ROC curve analysis for the diagnosis of HLH among our cohort is shown in Table 2 for each biomarker. The best AUC, representing the highest discrimination ability, were obtained for ferritin, IL-18, and glycosylated ferritin (in descending order). Sensitivity and specificity were provided for cutoff points with the highest Youden index. With a sensitivity set at 85%, ferritin, IL-18, and glycosylated ferritin were the biomarkers with the highest specificity (above 70%) in our cohort.

Comparison Between Serum Biomarkers and HScore

To assess the utility of these biomarkers as a HLH-screening parameter, we analyzed their correlation to the HScore. Most of the evaluated cytokines (sCD25, sCD14,sCD163, CXCL9, IL1–0, INF-ɣ, IL-6, IL-17α, IL-12p70, IL-1β, and IP-10) showed a poor correlation with the HScore (Spearman rank correlation coefficient, rs, ranged between − 0.16 and 0.32), except for ferritin (as expected since included in the score calculation), glycosylated ferritin, and IL-18 (rs = 0.59, − 0.41, and 0.46 respectively, $p < 0.0001$).

The best AUC was obtained for the HScore compared to all biomarkers individually tested (Table 2 and Fig. 2). Combining IL-18 with the HScore provided a new score with an increased specificity compared to the HScore alone. For the optimal cutoff value, IL18*HScore presented a diagnostic sensitivity and specificity of 93% and 96%, respectively (Table 2 and Fig. 3). With a sensitivity set at 100%, IL18*HScore presented a diagnostic specificity of 86% compared to 70% for the HScore alone (Fig. 3).

Principal Component Analysis

A multivariate analysis by PCA was performed with the 7 most relevant parameters. Principal components (PC) were mainly composed of IL-18, ferritin,sCD25, and glycosylated ferritin for PC1 and IL-17 and sCD14 for PC2. PC1 accounted for 43% of the variance of the data, PC2 for 19% of the variance (Fig. 4). The classification of the data based on this ACP highlighted 3 clusters of patients, one of which exclusively comprised 11 of the 14 HLH patients. This analysis revealed a distinct biomarker profile for HLH patients.

Differences in Cytokines' Pattern Depending on the Underlying Etiology for Secondary HLH

The distributions of inflammatory biomarkers among patients with malignancy-triggered HLH, infection-associated HLH, and without HLH are shown in Fig. 5.

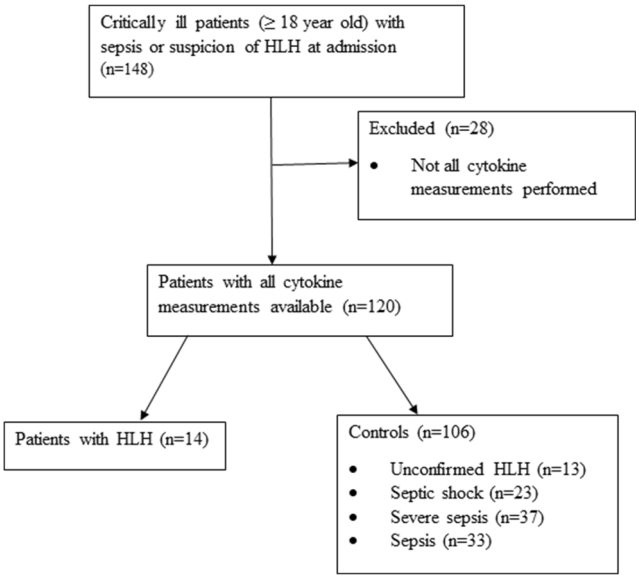

Fig. 1 Study flow chart

Four cytokines (IL-6, IL-17α, IL-12p70, and IL-1β) were excluded from further analysis as they were not different in HLH patients compared to controls (mainly septic patients in ICU).

Serum ferritin, glycosylated ferritin, and IL-18 were significantly elevated in HLH patients compared to the control group. The same trends were also observed for sCD25, sCD163, sCD14, and IL-10, with the highest values observed for malignancy-triggered HLH, the intermediate values observed for infection-associated HLH, and the lowest values observed in the control group.

Malignancy-triggered HLH patients had significantly elevated levels of INF-ɣ and CXCL9 compared to infection-associated HLH patients.The same trend was also observed for IP-10. The infection-associated HLH patients were comparable to the control group for these cytokines.

Discussion

These last years, many biomarkers have been proposed for the diagnosis of secondary HLH. However, a lack of comparative studies in adult patients was not conductive for a consensus on which biomarker was most sensitive and specific for the diagnosis of adult HLH. We therefore investigated the performances, for the early diagnosis of HLH, of a large panel of biomarkers including ferritin, glycosylated ferritin, and various cytokines, in a prospective cohort of adult patients suspected of HLH compared to septic patients admitted in ICU. This control group was chosen to evaluate the specificity of these biomarkers due to the well-known overlap of the clinical and laboratory features of HLH and sepsis. As we did not observe any significant differences in biomarker levels depending on sepsis severity (data not shown), we included these patients in the same control group for further analyses. We then identified biomarkers that could distinguish the underlying etiology of HLH.

Our results showed that in our cohort of critically ill adult patients, serum ferritin was the most discriminating parameter for early diagnosis of secondary HLH, compared to other biomarkers evaluated. These data support the interest of including ferritin into a sepsis laboratory panel, as mentioned by Lachmann et al. [22]. However, although the study of Naymagon et al. [8] considers that the ferritin threshold, used in HLH diagnostic criteria, is

Table 1 Characteristics of the study population

	HLH suspected patients ($n = 27$)		Sepsis patients ($n = 93$)		
Characteristic	HLH ($n = 14$)	Unconfirmed HLH ($n = 13$)	Sepsis ($n = 33$)	Severe sepsis ($n = 37$)	Septic shock ($n = 23$)
Male : female	10 (71) : 4 (29)	10 (77) : 3 (23)	20 (61) : 13 (39)	25 (68) : 12 (32)	15 (65) : 8 (35)
Age, median (interquartile range) (y)	52 (40–67)	52 (37–65)	62 (51–72)	60 (49–75)	67 (50–79)
Underlying disease					
Infection	6 (43)	4 (31)	33 (100)	31 (84)	21 (92)
Hematologic malignancy + infection	3 (21)	3 (23)	0 (0)	4 (11)	1 (4)
Solid cancer + infection	0 (0)	0 (0)	0 (0)	2 (5)	1 (4)
Postchemotherapy	0 (0)	3 (23)	0 (0)	0 (0)	0 (0)
Hematologic malignancy	4 (29)	3 (23)	0 (0)	0 (0)	0 (0)
Unknown	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)
HScore, median (interquartile range)	205 (160–232)	120 (67–140)	33 (19–52)	52 (33–82)	52 (33–76)

Values are presented as number (%) unless otherwise indicated. *HLH* hemophagocytic lymphohistiocytosis

Table 2 ROC curve analysis

	AUC	AUC 95% confidence interval	Cutoff (Youden index max): sensitivity (%)–specificity (%)	Cutoff (sensitivity 85%) : specificity (%)
IL-18*HScore	0.9849	0.9628 to 1.007	> 180,200 : 93–96	> 187,000 : 96
HScore	0.9671	0.9256 to 1.009	> 121: 93–89	> 126 : 91
Ferritin (μg/l)	0.9394	0.8820 to 0.9967	> 1799 : 93–82	> 2116 : 84
IL-18 (pg/ml)	0.9003	0.8115 to 0.9890	> 1961 : 79–87	> 1478 : 79
GF (%)	0.8484	0.7342 to 0.9626	< 19 : 64–95	< 40 : 71
sCD163 (ng/ml)	0.8275	0.7129 to 0.9421	> 2032 : 79–77	> 1543 : 65
sCD14 (pg/ml)	0.7743	0.6409 to 0.9077	> 4022 : 64–82	> 2861 : 59
IL-10 (pg/ml)	0.7608	0.6118 to 0.9098	> 11 : 64–84	> 2543 : 51
CXCL9 (pg/ml)	0.7540	0.5790 to 0.9291	> 514 : 64–91	> 109 : 35
sCD25 (pg/ml)	0.7385	0.5590 to 0.9181	> 16,208 : 57–94	> 2207: 23
IL-17A (pg/ml)	0.7123	0.5759 to 0.8486	< 3805 : 64–76	< 12.5 : 37
IFN-γ (pg/ml)	0.6914	0.5439 to 0.8388	> 245 : 43–93	> 6317 : 40
IP-10 (pg/ml)	0.6725	0.5182 to 0.8268	> 5295 : 36–95	> 305 : 38
IL-12p70 (pg/ml)	0.5984	0.4418 to 0.7550	> 1828 : 71–56	> 1174 : 31
IL-1β (pg/ml)	0.5590	0.4029 to 0.7150	> 0.325 : 57–61	> 0.091 : 22
IL-6 (pg/ml)	0.5492	0.4217 to 0.6767	< 44.3 : 79–45	< 69 : 34

AUC area under the curve, *GF* glycosylated ferritin, *s* soluble

too low to be clinically relevant in adults, we observed an optimal ferritin cutoff around 2000 μg/l, equivalent to that used in the HScore [6]. Increasing this cutoff, based on observations obtained in unselected population, i.e., a population with low pretest probabilities for HLH, could delay the diagnosis of HLH and the initiation of adequate therapy before a potential fatal evolution of the disease.

We confirmed that the HScore presents a good diagnostic accuracy (the highest AUC compared to other biomarkers tested individually) in critically ill patients, even early in the course of HLH, as shown by Knaak et al. [23]. The time of score assessment differs between our study and Knaak et al.'s. Indeed, they are recorded at the day of maximum levels of ferritin in Knaak et al. rather than within the first 24 h of ICU admission in our study. This could also explain the difference observed between the optimal cutoff for HScore. It is lower in our study (77 compared to 168) to obtain the same sensitivity of 100%.

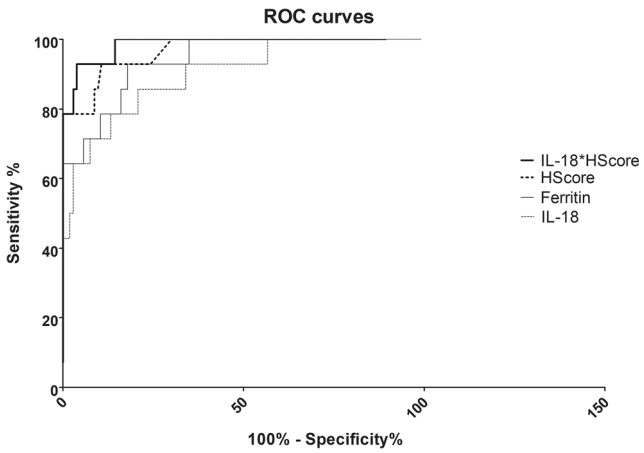

Fig. 2 Receiver operating characteristic curve analysis of the most discriminating biomarkers and scores for diagnosis of adult hemophagocytic lymphohistiocytosis

Interestingly, in order to diagnose HLH as early as possible in critically ill adult patients, we highlighted a new score, IL-18*HScore, resulting from the combination of HScore and IL-18, which results in an increased diagnostic specificity: from 70% for the HScore to 86% for the new score, for the same sensitivity of 100% in our cohort. IL-18 is best known to increase INF-ɣ production by CD-8 T cells and NK cells and has primarily been studied in macrophage activation syndrome (HLH secondary to rheumatic diseases, MAS). Weiss et al. reported a correlation between chronic elevation of IL-18 and MAS risk in patients with hyperferritinemic and autoinflammatory diseases [12]. They also suggested that IL-18 could be an important host susceptibility factor in some infection-associated HLH patients. Our data highlighted the potential role of IL-18 as an early increased biomarker in adult secondary HLH (associated with malignancy or infection). Moreover, we confirmed that a low percentage of glycosylated ferritin (< 20%) [10] had a high specificity (95%) for the diagnosis of HLH among critically ill patients but with insufficient sensitivity to be a relevant screening tool. Compared to ferritin and IL-18, sCD25, sCD14, and sCD163 are, in

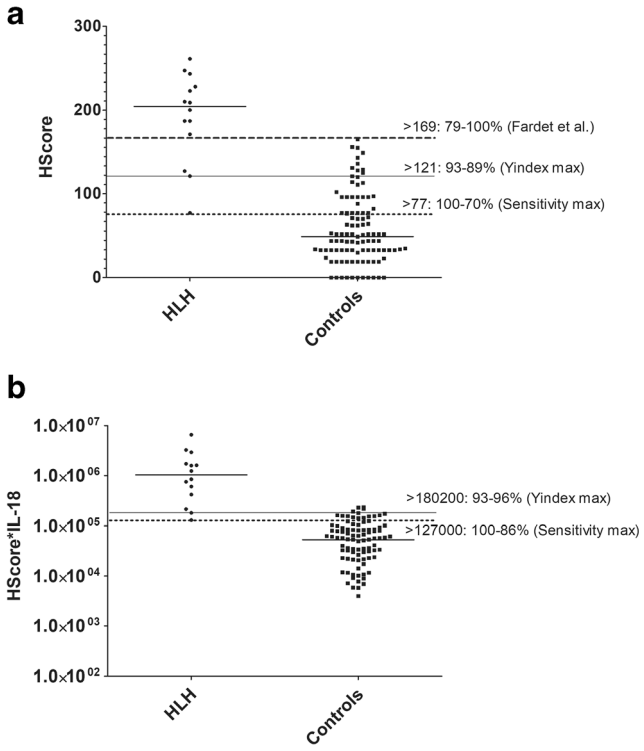

Fig. 3 **a** HScore and **b** HScore*IL18 levels for patients with HLH and control patients (patients with sepsis and unconfirmed HLH). Each point represents a single patient, and the short line in the distribution of the points represents the median level for the corresponding group. The dotted lines indicate the cutoff with the maximal sensitivity, and the solid lines indicate the optimal cutoff (Yindex max). The dashed line indicates the cutoff of Fardet et al. for HScore. Diagnostic sensitivity and specificity are indicated for each cutoff. *HLH* hemophagocytic lymphohistiocytosis

our experience, only of limited interest for the diagnosis of secondary HLH in adults.

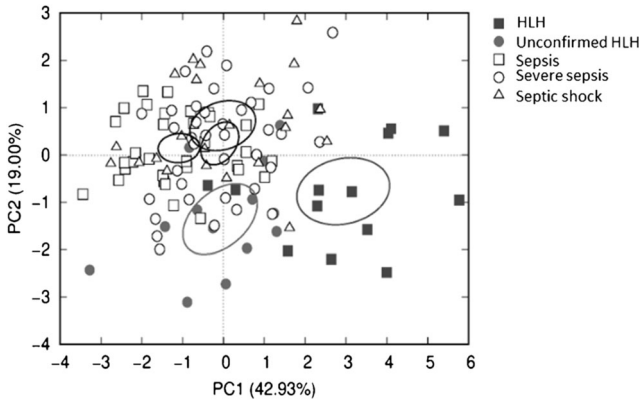

Fig. 4 Principal component analysis (PCA) of the 7 most relevant biomarkers. The membership of individual data is indicated using filled square (HLH patients), filled circle (unconfirmed HLH), open square (patients with sepsis), open circle (patients with severe sepsis), and open triangle (patients with septic shock). Data that can be associated in different clusters are delineated (ellipses). The ellipses correspond to the confidence ellipses (level 0.95) around the centroid of each patient type. The proportion of variance captured is given as a percentage for both the first and second principal components (PC1 and PC2)

Despite the limited number of HLH patients in this study, we observed, very early in the course of the disease, a distinct cytokine profile between malignancy-triggered HLH and HLH associated with infection. Patients with HLH triggered by malignant disease exhibited higher levels of IFN-γ, also reflected by very high levels of CXCL9 (chemokine induced by IFN-γ) compared to infection and sepsis-associated HLH, for whom no differences were observed. Moreover, the infection-associated HLH patients had a much lower increase in IL-18 production (IFN-γ inducing factor) compared to malignancy-triggered HLH patients. These observations are consistent with the review by Carcillo and Shakoory [24] which summarizes the same differences observed between the cytokine patterns in sepsis-related HLH (weakly increased IL-18, low IFN-γ) and in MAS and familial HLH (very high IL-18 and high IFN-γ). This illustrates once again that although IFN-γ is a critical driver of HLH leading to hemophagocytosis, secondary HLH may also develop in an independent manner. Ferritin is no longer considered a bystander which is highly increased in HLH but could play an active role, in the pathogenesis of secondary HLH especially in extreme hyperferritinemia [25]. According to this model, ferritin acts as a mediator in a positive feedback loop involving inflammasome activation and production of IL-1, IL-18, and high levels of extracellular ferritin, leading to liver injury, innate immune cell activation, and depression of adaptive immune cell. Further investigations should highlight the mechanisms associated with different cytokine patterns and will probably guide therapeutic strategies.

However, the interpretation of the biomarker levels determined at a given point in time remains challenging as these levels can change rapidly throughout the course of the disease, so that scores should be regularly reassessed, particularly for critically ill patients with deteriorating conditions. Moreover, concerning serum cytokine testing, we must take into account that some key cytokines could only be secreted locally (as instance for IL-1B), and thus, variation in levels are not identifiable in outside tissues.

In conclusion, this is the largest study available to date, comparing diagnostic biomarkers for HLH on a cohort of critically ill adult patients. Serum ferritin was the most discriminating parameter for early diagnosis of secondary HLH. IL18*HScore was identified as a highly potential score with diagnostic sensitivity and specificity reaching 93 and 96%.

We have also demonstrated that through a deeper knowledge of the mediators involved in the pathophysiology of the various forms of HLH, it would undoubtedly be possible to establish an earlier diagnosis and to more quickly adapt the therapeutic strategy.

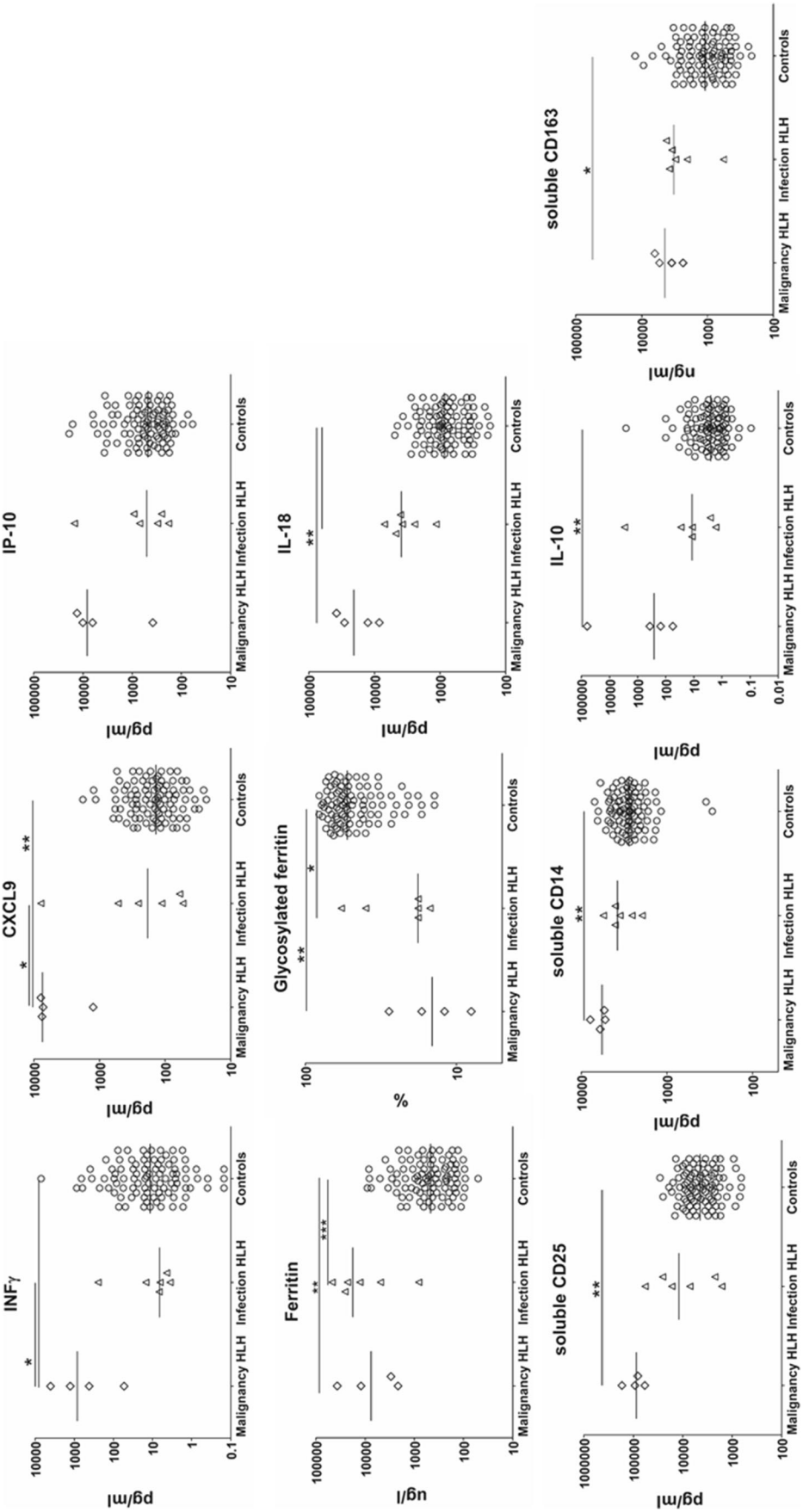

Fig. 5 Inflammatory biomarkers' levels in different patient groups: malignancy-triggered HLH, HLH associated with infection, and controls (patients with infection or malignancy). Bars represent median values. Statistically significant differences among the patient groups are shown as $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$. *HLH* hemophagocytic lymphohistiocytosis

Author Contribution F.D. and F.C. designed the experiments. F.D., B.M., and C.N. performed the experiments. F.D., M.V., P.B., and F.C. analyzed the data. N.M., D.DB., F.W., P.G., and A.S. recruited the patients and analyzed clinical data. F.D., B.M., and F.C. wrote the manuscript. All authors read, revised, and approved the manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors have disclosed that they do not have any conflicts of interest.

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