Challenges in Identifying Hemophagocytic Lymphohistiocytosis in the ICU*

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Hemophagocytic lymphohistiocytosis (HLH) is an elusive disease with a grim prognosis. Many HLH patients develop respiratory failure and shock requiring critical care support, and early recognition and management by an intensivist are important for improving outcomes.

HLH is an inflammatory syndrome rather than a distinct disease, and is a result of immune dysregulation. HLH patients often present with fever, shock, and multiple organ failure necessitating ICU admission (1). In primary or familial HLH, impaired function of cytotoxic (CD8+) T cells and natural killer (NK) cells leads to persistent macrophage activation via interferon-gamma signaling (2). In secondary or acquired HLH, it has been postulated that constant stimulation of the immune system in the setting of infection, malignancy, or autoimmune disease may lead to secretion of excessive cytokines (3). A vast majority of HLH seen in adults is secondary or acquired HLH, although recent data suggest that some adults may have familial HLH genetic mutation variants that predispose to HLH (1).

In the largest global epidemiologic study of 2,197 patients with secondary HLH, the underlying trigger was identified as infection and/or malignancy in a vast majority of the patients; most of the patients were from East Asia, with a high number of patients with NK-T cell tumors resulting in a skewed demographic (4). Data from a single center at Johns Hopkins is more representative of the western population of HLH, with over 1/3 associated with malignancy, less than 1/3 associated with infection, approximately 15% associated with Epstein-Barr virus (EBV), 10% from autoimmune diseases, and 10% with idiopathic triggers (5).

The Histiocyte Society established diagnostic criteria for acquired HLH, and patients must demonstrate at least five of the following eight features: 1) fever, 2) splenomegaly, 3) cytopenias in at least two cell lines, 4) hypertriglyceridemia or hypofibrinogenemia, 5) elevated soluble interleukin (IL)–2 receptor, 6) decreased or absent NK cell activity, 7) ferritin elevation, and 8) hemophagocytosis in tissue (6). Despite the name of the disease, the presence of hemophagocytosis in the marrow, or any other tissue, is the least reliable and most variable finding (5). Some of these tests, namely soluble IL-2 receptor and the NK cell activity assay, are send-out tests at most institutions with a long turnaround time. There is no single pathognomonic finding of HLH, and this can often make it challenging to distinguish HLH from other causes of critical illness in the ICU, such as sepsis.

One of the diagnostic criterion of HLH is a ferritin greater than or equal to 500 µg/L, however, it can be challenging to interpret ferritin values in the ICU since a high ferritin can be seen in many critically ill patients as an acute phase reactant. Studies have previously demonstrated that a high ferritin value correlates with mortality (7). In a recent study published in *Shock*, 2,623 out of 6,340 ICU patients (41.4%) at a single institution had a ferritin elevation over 500 µg/L, but only 40 of those patients had HLH (8).

In this issue of *Critical Care Medicine*, the authors of the above *Shock* study used the identical database to retrospectively assess the ferritin levels in ICU patients to determine if the ferritin value correlated with HLH diagnosis, or other etiologies of illness by Lachman et al (9). Over a 12-year period at a single center, 2,623 patients were identified with a ferritin greater than or equal to 500 µg/L, and among those patients 40 (1.52%) were characterized as having HLH, while the other patients were classified as having sepsis with or without shock, or an alternative diagnosis. A 10-fold higher ferritin was noted in patients with HLH when compared with those without. The authors determined a ferritin cutoff of 9,083 µg/L correlated with a high specificity (91.9%) and sensitivity (92.5%) for HLH in the ICU (9). Their finding is similar to a pediatric study of 330 patients (10 with HLH) wherein a ferritin cutoff of greater than 10,000 µg/L was 90% sensitive and 96% specific for HLH (10).

The authors suggest that a higher ferritin value in ICU patients may help differentiate between HLH and sepsis; however, high ferritin values are seen in a number of diseases. A retrospective study from the Partners Healthcare System noted that very high ferritin values were more commonly seen in patients with renal failure and hepatocellular injury, rather than in HLH (11). In that study, the median ferritin at diagnosis in adult patients with HLH was 5,823 µg/L in 50 patients,

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although the study does not note how many of these patients required ICU care (11). Another Spanish prospective cohort study followed 151 patients with HLH and noted a ferritin greater than or equal to 10,000 µg/L in only 34.3% of the patients, although only 59 of the 151 patients were treated in an ICU, and so perhaps the sicker patients may have had higher ferritin values (12).

Among patients with HLH, higher ferritin values also suggest worse outcomes. In addition to using the ferritin value for diagnosis, in the above-mentioned study in *Shock*, the authors compared the ferritin values within those 40 HLH patients as a prognostic marker, and noted a difference in the ferritin value at diagnosis between survivors (16/40) and nonsurvivors ($p = 0.021$), and in the minimum ferritin value (2,195 µg/L in survivors vs 9,759 µg/L in nonsurvivors; $p = 0.001$). Ferritin, along with the soluble IL-2 receptor, is often used as a marker for HLH response, and patients with higher ferritin values are less likely to survive (1). A serum ferritin in HLH can be useful in diagnosis, prognosis, following treatment responses, and perhaps, as the study by Lachman et al (9) suggests, in differentiating between HLH and other critical illness, such as sepsis. Both HLH and sepsis can present with shock and multiple organ dysfunction, and of course, ongoing sepsis may trigger HLH, or an HLH patient on treatment may develop sepsis further complicating distinction.

It is clear that better identification of HLH patients is necessary, and this may be achieved by incorporating more sensitive markers into routine clinical use. Recently Cui et al (13) measured soluble CD163 (a monocyte/macrophage activation marker) as a possible additional marker for the recognition of HLH. Another group reported significantly higher monocyte human leukocyte antigen (HLA)-DR expression in a single patient with HLH when compared with patients with sepsis (14). In the most updated guidelines from the Histiocyte Society, other markers that may be more suggestive of HLH include elevated bilirubin, transaminases, hepatomegaly, elevated lactate dehydrogenase, and D-dimer levels, and some of these markers are included in the H-score, a validated tool for predicting the probability of HLH (15). In addition, a cytokine pattern of elevated interferon-γ and IL-10 with only mild elevation in IL-6 may correlate with patients having secondary HLH (1).

Once a diagnosis of secondary HLH is established, the goal is to treat the underlying trigger, that is, malignancy, infection, or autoimmune disease (5). High dose steroids and chemotherapy are used in critically ill patients requiring urgent treatment of HLH (1). Other treatment options include immunoglobulins, alemtuzumab (an anti CD52 antibody), anti-thymocyte globulin, anakinra (IL-1 receptor antagonist), tocilizumab (anti-IL–6 receptor antibody), rituximab (anti-CD20 antibody; used in Epstein-Barr virus disease), ruxolitinib (Janus kinase inhibitor), and most recently emapalumab (anti-interferon–γ antibody) (1).

Despite the inherent limitations of a single-center retrospective study, the article by Lachman et al (9) is the largest review of ICU patients with HLH. HLH remains a morbid disease with a mortality rate greater than 60% (12). Even with the challenges in identifying patients with HLH, over the past decade more patients have been diagnosed with HLH as more physicians are becoming aware of the disease. The study by Lachman et al (9) presents an important finding of markedly elevated ferritin in ICU patients with HLH when compared with other ICU patients with sepsis. The first step in improving outcomes and mortality must start with diagnosis, and the study by Lachman et al (9) is a step in that direction.

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Hyperferritinemia in Critically Ill Patients*

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Objective: Hyperferritinemia is frequently seen in critically ill patients. A rather rare though life-threatening condition related to severely elevated ferritin is hemophagocytic lymphohistiocytosis. We analyze ferritin levels to differentiate hemophagocytic lymphohistiocytosis from other causes of hyperferritinemia in a mixed cohort of critically ill patients.

Design: Retrospective observational study.

Setting: Adult surgical, anesthesiologic, and medical ICUs of a university hospital.

Patients: Critical care patients (≥ 18 yr old) admitted to any of the adult ICUs at Charité – Universitätsmedizin Berlin between January 2006 and August 2018 with at least one ferritin value and hyperferritinemia (≥ 500 µg/L).

Interventions: None.

Measurements and Main Results: Patients were categorized into hemophagocytic lymphohistiocytosis, sepsis, septic shock, and other diagnoses. These were further categorized into 17 subgroups. Hemophagocytic lymphohistiocytosis diagnosis was based on Hemophagocytic Lymphohistiocytosis-2004 criteria and the HScore. Of 2,623 patients with hyperferritinemia, 40 were considered to have hemophagocytic lymphohistiocytosis (1.52%). Maximum ferritin levels were highest in hemophagocytic lymphohistiocytosis patients compared with all other disease groups (each $p < 0.001$). Sepsis and septic shock patients had higher maximum ferritin levels than patients with other diagnoses (each $p < 0.001$). A maximum ferritin value of 9,083 µg/L was at 92.5% sensitivity and 91.9% specificity for hemophagocytic lymphohistiocytosis (area under the curve, 0.963; 95% CI, 0.949–0.978). Of all subgroups with other diagnoses, maximum ferritin levels were highest in patients with varicella-zoster virus, hepatitis, or malaria (median, 1,935, 1,928, and 1,587 µg/L, respectively). Maximum ferritin levels were associated with increased in-hospital mortality (odds ratio, 1.518 per log µg/L [95% CI, 1.384–1.665 per log µg/L]; $p < 0.001$).

Conclusions: This is the largest study of patients with ferritin available in a mixed ICU cohort. Ferritin levels in patients with hemophagocytic lymphohistiocytosis, sepsis, septic shock, and other conditions were distinctly different, with the highest ferritin levels observed in hemophagocytic lymphohistiocytosis patients. Maximum ferritin of 9,083 µg/L showed high sensitivity and specificity and, therefore, may contribute to improved diagnosis of hemophagocytic lymphohistiocytosis in ICU. The inclusion of ferritin into the sepsis laboratory panel is warranted. (*Crit Care Med* 2020; 48:459–465)

Key Words: ferritin; hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; hyperferritinemia; intensive care unit; macrophage activation syndrome; mortality

*See also p. 599.

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Ferritin is an acute-phase reactant, commonly triggered by inflammation and infection. Accordingly, elevated serum ferritin is often found in septic patients, where it is related to worse clinical outcome (1, 2). Other conditions associated with hyperferritinemia include chronic kidney disease, malignancies, particularly hemato-oncologic neoplasias, liver diseases, chronic alcohol consumption, and metabolic syndrome (3, 4).

Elevated ferritin is also seen in states of iron overload either due to blood transfusions or due to hemochromatosis, and in rather rare conditions such as hereditary hyperferritinemia and hemophagocytic lymphohistiocytosis (HLH) (4, 5). The predictive value of ferritin as a potential marker for clinical outcome in the critically ill has been described by Bobbio-Pallavicini et al (6), who found an increase in ferritin to be associated with a deteriorating clinical condition. Further research conducted by Bennett et al (7) demonstrated that ferritin levels greater than 3,000 µg/L were related to ICU admission and increased mortality in pediatric patients, whereas Unal et al (8) identified elevated ferritin as an independent risk factor for death in adult ICU patients. Furthermore, a decrease in ferritin concentrations predicts clinical response in septic patients (9). In patients with HLH who commonly share clinical characteristics with septic patients, hyperferritinemia is one of eight diagnostic criteria according to the HLH-2004 criteria and is seen as an important diagnostic marker (10–13). Triggered by infections, malignancies, or autoimmune disorders, secondary HLH is characterized by toxic immune activation, leading to uncontrolled inflammation where extreme hyperferritinemia is observed. Due to a similar clinical presentation as sepsis, HLH in critically ill patients often remains undiagnosed, highlighting the relevance of accurate diagnostic markers (14). However, the optimal ferritin cutoff for HLH diagnosis in adult critically ill patients remains controversial, particularly to distinguish HLH from sepsis (15). An elevated ferritin of greater than 500 µg/L, as proposed by the Histiocyte Society, provides inadequate diagnostic specificity in adult HLH patients, as multiple conditions related to any type of inflammation can cause increased ferritin in the critical care setting (16). Small studies, determining prediction accuracy of ferritin for HLH diagnosis, revealed markedly higher thresholds. In adult ICU patients, our research group as well as Saeed et al (11) reported an optimal ferritin level of 3,095 µg/L and 3,951 µg/L, respectively (14). Barba et al (17) detected a median ferritin of 10,600 µg/L in their cohort of 71 adult HLH patients admitted to the ICU. Yet, concerns have been raised that even severely elevated ferritin is not as sufficiently pathognomonic for HLH as it is an unspecific marker of multiple processes including inflammation, iron overload, and renal and hepatic failure (9, 15, 18, 19). Of note, Schram et al (18) found hemolytic anemia as the only condition to be independently associated with an increase in ferritin. As elevation of ferritin is commonly seen in the critical care setting and HLH is a rare diagnosis, its positive predictive value for HLH diagnosis is rather low (5, 15).

Given the wide variety of etiologies underlying hyperferritinemia, the importance of ferritin in diagnosis of HLH, and the paucity of available data for ICU patients, our aim was to investigate the distribution of ferritin levels and associated conditions such as HLH, septic shock, sepsis, and other diagnoses in a large cohort of multidisciplinary ICU patients at an academic medical center to determine the ferritin cutoff best predictive for HLH in ICU.

METHODS

Patients

This retrospective observational study was performed at the Charité – Universitätsmedizin Berlin. Data of ICU patients who were admitted to at least one of our adult surgical, anesthesiologic, or medical ICUs between January 2006 and August 2018 were extracted from two electronic patient data management systems operated at the Charité – Universitätsmedizin Berlin (COPRA, Sasbachwalden, Germany; and SAP, Walldorf, Germany). All patients 18 years old or older with at least one ICU ferritin value and hyperferritinemia of at least 500 µg/L in line with the HLH-2004 criteria (10) were included in the study. The study period was defined from admission to the ICU until hospital discharge, transfer, or death. As part of a post hoc analysis, we additionally searched all included patients for soluble interleukin 2 receptor (sIL-2R) as one of the other HLH-2004 criteria. In patients with multiple ferritin measurements, the highest ferritin value was considered for further analysis. The same applied to sIL-2R measurements.

Diagnosis of HLH, Sepsis, Septic Shock, and Other Diagnoses

As a first step, we searched the *International Classification of Diseases*, 10th Edition (ICD-10) codes (for HLH D76.1, D76.2, and D76.3) as well as the records of all patients for clinically diagnosed or suspected HLH, that were then reviewed by two HLH experts who confirmed or rejected the diagnosis. Only cases suspected or diagnosed with HLH by the clinicians were reviewed by the experts, which was according to the HLH-2004 criteria (10), at present the gold standard for HLH diagnosis, and the HScore (20) while taking into account patients' history and clinical judgment (21). Of note, HLH patients include seven previously undiagnosed cases of HLH who have been retrospectively diagnosed and published by our research group (14). In a second step, we divided all non-HLH patients into three groups based on their ICD-10 codes: sepsis (A22.7, A39.1, A39.2, A39.3, A39.4, A40.-, A41.-, B37.7, O08.2, O75.3, O85, O88.3, R65.0, R65.1, T80.2, T81.4, T88.0; all without R57.2), septic shock (R57.2), and other diagnoses. In a third step, all patients with other diagnoses were allocated to 17 groups: liver disease, renal disease, autoimmune disease, hepatitis, tuberculosis, human immunodeficiency syndrome (HIV), Herpes simplex virus, *Cytomegalovirus*, Epstein-Barr virus, varicella-zoster virus (VZV), influenza, malaria, (bacterial/viral/fungal) infection, inflammation without infection, hematologic malignancy, solid tumors, and history of (stem cell/organ) transplantation (for ICD-10 codes of all groups, see **Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F170).

Statistical Analysis

Results are shown as median ± quartiles or percentage, respectively. Differences between patients with HLH, sepsis, septic shock and other diagnoses, respectively, were calculated using Kruskal-Wallis test for continuous data and the chi-square test for qualitative data. Receiver operating characteristics (ROC)

analyses were performed to analyze best maximum ferritin levels and maximum sIL-2R to predict HLH and in-hospital mortality, respectively. As a post hoc analysis to test the predictive value of maximum ferritin to distinguish between two disease groups, we used repetitive multivariable logistic regression models adjusting for age, sex, body mass index (BMI), and maximum Sequential Organ Failure Assessment (SOFA) score with diagnoses as binary outcome variables (e.g., HLH vs septic shock, HLH vs sepsis, etc). In addition, ROC analyses were used to find the best maximum ferritin levels to differentiate between the respective cohorts. Multivariable logistic regression analysis was performed to analyze the influence of maximum ferritin on in-hospital mortality while adjusting for age, sex, BMI, diagnoses (categorical HLH/sepsis/septic shock/other), and maximum SOFA score. For all regression analyses, the natural logarithm of maximum ferritin values was used due to skewed data. SPSS 25.0 software (IBM, Armonk, NY) was used for all statistical analysis. A p value of less than 0.05 was considered statistically significant.

Ethics

Ethics approval was obtained from the institutional review board (Ethikkommission der Charité – Universitätsmedizin Berlin, EA1/176/16). The study was registered with www.ClinicalTrials.gov (NCT02854943) on August 1, 2016.

RESULTS

Study Population and Outcome

In total, 116,310 patients were admitted to the ICUs between January 2006 and August 2018. Of these, 6,340 patients were 18 years old or older and had at least one ferritin measurement during their ICU stay. Ferritin was elevated (≥ 500 µg/L) in 2,623 patients, who were, therefore, finally analyzed (**Supplemental Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F171; **legend**, Supplemental Digital Content 6, http://links.lww.com/CCM/F175). Fifty of 2,623 patients had initially been diagnosed or suspected as HLH, of whom 40 were confirmed as HLH by the experts (n = 40 [1.52%]). For diagnosis of HLH, median 5 of 8 HLH-2004 criteria were fulfilled (minimum–maximum range, 3–7), whereas median HScore was 224 (minimum–maximum range, 133–302). For detailed description of all 40 HLH patients (Knaak et al [22]). Of the remaining 2,583 patients, 1,003 had sepsis without shock, 626 were diagnosed with septic shock, and 954 had other diagnoses. Five hundred ninety-six patients had more than one ferritin measurement (22.7%). **Figure 1** depicts the distribution of all maximum ferritin levels in relation to patient numbers. Basic patient characteristics, biomarkers, and outcome parameters are shown in **Table 1**.

Serum Ferritin in HLH, Sepsis, Septic Shock, and Other Diagnoses

Over all groups, maximum ferritin levels differed significantly between all major patient groups ($p < 0.001$) (**Fig. 2**). Maximum ferritin levels were higher in HLH patients compared with patients with septic shock, sepsis, or other diagnosis (each $p < 0.001$). In sepsis and septic shock patients, maximum ferritin levels were higher than in patients with other diagnoses (each $p < 0.001$). When comparing sepsis and septic shock patients, maximum ferritin levels were higher in the latter group (median, 1,448 vs 1,545 µg/L; $p = 0.001$). Considering only patients with other diagnoses, **Table 2** shows the median of the patients' maximum ferritin values in various disease entities, with highest ferritin levels seen in patients with VZV, hepatitis, or malaria. In multivariable logistic regression analyses, ferritin was found as a good marker to distinguish HLH from septic shock, sepsis, and other diseases, but as poor marker to differentiate septic shock from sepsis or other diseases (**Supplemental Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/F172).

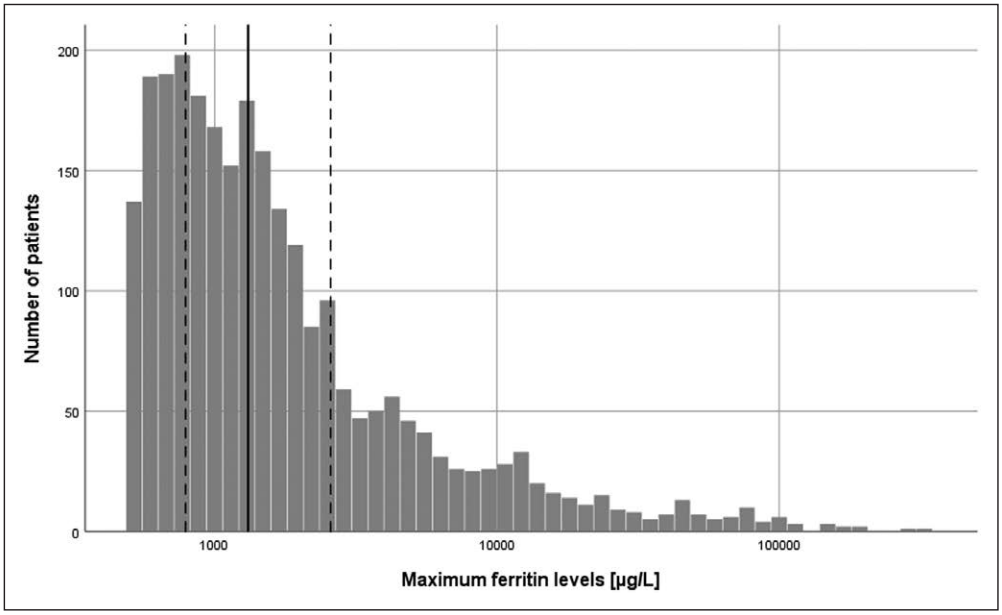

Figure 1. Histogram of all 2,623 maximum ferritin measurements. Ferritin median 1,314 µg/L (*solid line*), percentiles (25–75%; *dashed line*): 788 µg/L and 2,576 µg/L. For visualization, *x*-axis is plotted in logarithmic scale.

Ferritin and sIL-2R for Diagnosis of HLH

ROC analysis identified a ferritin of 9,083 µg/L as predictive for HLH with 92.5% sensitivity and 91.9% specificity (AUC, 0.963; 95% CI,

TABLE 1. Basic Patient Characteristics, Biomarkers, and Outcome Parameters

Parameters	Hemophagocytic Lymphohistiocytosis (*n* = 40)	Septic Shock (*n* = 626)	Sepsis Without Shock (*n* = 1,003)	Other (*n* = 954)	*p*
Age (yr)	47 (33–62)	59 (46–71)	63 (49–72)	64 (51–74)	< 0.001[a]
Male sex, *n* (%)	26 (65.0)	405 (64.7)	617 (61.5)	566 (59.3)	0.186[b]
Body mass index (kg/m^2)	23.0 (21.0–26.5)	24.5 (22.0–28.5)	25.0 (22.0–29.3)	24.6 (22.0–28.0)	0.105[a]
Maximum ferritin (µg/L)	31,674 (15,121–87,975)	1,545 (964–4,175)	1,448 (836–2,803)	974 (696–1,795)	< 0.001[a]
Maximum soluble interleukin 2 receptor (U/mL)[c]	7,072 (3,159–13,743)	2,571 (1,483–5,856)	1,761 (1,045–5,231)	2,586 (991–4,294)	0.001[a]
Sepsis without shock, *n* (%)	12 (30.0)	0	1,003 (100)	0	< 0.001[b]
Septic shock, *n* (%)	23 (57.5)	626 (100)	0	0	< 0.001[b]
Hemodialysis, *n* (%)	29 (72.5)	451 (72.0)	570 (56.8)	336 (35.2)	< 0.001[b]
Extracorporeal lung assist/extracorporeal membrane oxygenation, *n* (%)	6 (15.0)	92 (14.7)	71 (7.1)	25 (2.6)	< 0.001[b]
ICU admission SOFA score	9 (6–13)	8 (5–12)	6 (3–10)	4 (2–7)	< 0.001[a]
Maximum SOFA score	17 (12–19)	15 (12–18)	12 (9–15)	7 (4–11)	< 0.001[a]
ICU duration (d)	20.0 (11.3–37.3)	32.9 (12.7–72.3)	26.5 (10.0–58.0)	8.0 (3.0–22.0)	< 0.001[a]
Inpatient duration (d)	27.7 (18.6–77.4)	54.8 (26.3–103.7)	52.3 (27.0–87.6)	22.8 (11.0–41.9)	< 0.001[a]
Deceased, *n* (%)	24 (60.0)	273 (43.6)	326 (32.5)	142 (14.9)	< 0.001[b]

SOFA = Sequential Organ Failure Assessment.

[a]*p* values calculated using the Kruskal-Wallis test as appropriate.

[b]*p* values calculated using the χ^2 test as appropriate.

[c]Only available in 30 of hemophagocytic lymphohistiocytosis patients, in 31 patients with septic shock, in 26 patients with sepsis, and in seven patients with other diseases.

Continuous quantities in median with quartiles.

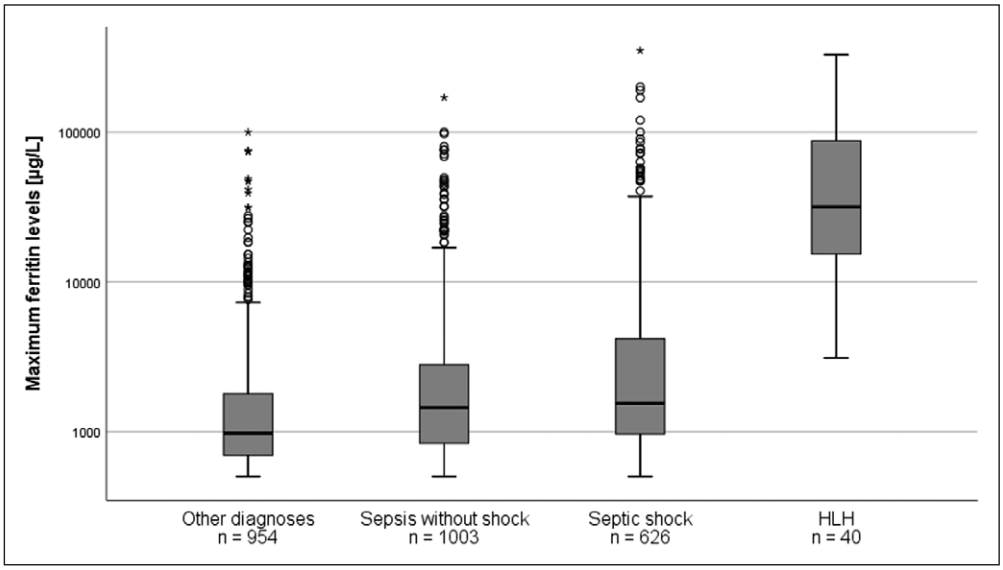

Figure 2. Distribution of maximum ferritin measurements between disease groups. Patients were categorized as hemophagocytic lymphohistiocytosis, septic shock, sepsis, and other diagnosis. Boxplots show median with quartiles (25–75%). *Whiskers* below and above show minimum and maximum values, respectively. Maximum ferritin values differed significantly between the four groups ($p < 0.001$). For visualization, *y*-axis is plotted in logarithmic scale.

0.949–0.978; **Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/F173; legend, Supplemental Digital Content 6, http://links.lww.com/CCM/F175). Sensitivity and specificity of various thresholds are shown in **Supplemental Table 3** (Supplemental Digital Content 5, http://links.lww.com/CCM/F174). For all 94 available sIL-2R values, ROC analysis showed a value of 4,621 U/mL to be predictive for HLH with 66.7% sensitivity and 76.6% specificity (AUC, 0.752; 95% CI, 0.650–0.853; Supplemental Fig. 2, Supplemental Digital Content 4, http://links.lww.com/CCM/F173;

TABLE 2. Maximum Serum Ferritin in Different Disease Entities of Patients With Other Diagnoses

Disease Entities	No. of patients	Maximum Serum Ferritin (µg/L)
Varicella-zoster virus	7	1,935 (752–2,691)
Hepatitis	58	1,928 (793–3,391)
Malaria	2	1,587 (888 to not applicable due to small number of patients)
Herpes simplex virus	17	1,462 (831–2,153)
Acute or chronic liver disease	205	1,435 (817–3,754)
Influenza	8	1,429 (916–1,547)
Cytomegalovirus	22	1,269 (850–2,591)
History of stem cell/organ transplantation	110	1,227 (808–2,467)
HIV	18	1,216 (853–1,760)
Tuberculosis	7	1,198 (752–3,131)
Epstein-Barr virus	6	1,172 (829–5,274)
Acute or chronic renal disease	583	1,034 (713–1,878)
Bacterial, viral, or fungal infection	717	996 (702–1,777)
Inflammation without infection	279	981 (692–1,759)
Autoimmune disease	73	953 (708–1,687)
Solid malignancy	148	905 (692–1,748)
Hematologic malignancy	70	846 (653–1,680)

Continuous quantities in median with quartiles. Due to various number of *International Classification of Diseases* codes in each single patient, patients might overlap between disease groups.

legend, Supplemental Digital Content 6, http://links.lww.com/CCM/F175).

Ferritin as Prediction Marker of Mortality

Multivariable regression analysis including age, sex, BMI, maximum SOFA score, and diagnosis as confounders revealed statistically significant associations between maximum ferritin concentrations and in-hospital mortality (**Table 3**). The ROC curve showed only low discrimination ability for maximum ferritin on in-hospital mortality as measured by the AUC of 0.655 (95% CI, 0.631–0.679).

DISCUSSION

This is the first study describing the clinical characteristics of severe hyperferritinemia in a mixed ICU cohort, including 40

TABLE 3. Multivariable Logistic Regression Analysis for In-Hospital Mortality

Covariates	OR (95% CI)	*p*
Age (yr)	1.025 (1.018–1.031)	< 0.001
Sex (male)	0.900 (0.740–1.094)	0.289
Body mass index	0.984 (0.970–0.998)	0.027
Ferritin maximum (log µg/L)	1.518 (1.384–1.665)	< 0.001
Sequential Organ Failure Assessment maximum	1.140 (1.116–1.164)	< 0.001
Diagnoses		
Other[a]	–	< 0.001
Sepsis	1.622 (1.270–2.071)	< 0.001
Septic shock	1.818 (1.375–2.403)	< 0.001
Hemophagocytic lymphohistiocytosis	1.444 (0.664–3.141)	0.354

OR = odds ratio.

[a]Reference. Multivariable logistic regression analysis was performed with in-hospital death as a dependent variable. For this purpose, the natural logarithm of maximum serum ferritin was used due to skewed data. Diagnoses were classified as other, sepsis, septic shock, and hemophagocytic lymphohistiocytosis.

HLH cases. Furthermore, it is currently the largest report of ICU patients with ferritin levels available who had a broad spectrum of underlying diseases. We observed statistically significant differences in ferritin levels among patients with HLH, sepsis, septic shock, and other disease states. Among these groups, HLH patients had the highest ferritin levels; a cutoff of 9,083 µg/L revealed the highest sensitivity (92.5%) and specificity (91.9%) for the diagnosis of HLH. Comparing sepsis and septic shock patients only, ferritin values were higher in septic shock patients. Analyzing conditions associated with hyperferritinemia other than HLH, sepsis, and septic shock, those with highest ferritin levels were VZV, hepatitis, and malaria.

Hyperferritinemia is frequently seen in the ICU in response to malignant, liver, renal, or inflammatory disorders (1, 5, 6, 11, 15). Among the latter, sepsis is one of the most common causes. However, also HLH should be considered as a differential diagnosis, albeit a rare one, especially in the case of nonresponsiveness to anti-infective treatment, cytopenias, prolonged fevers, or organomegaly. Overlap in clinical features is challenging in differentiating HLH from sepsis. Fever, cytopenias, and hyperferritinemia can be present in both. However, those findings do not confirm nor rule out either HLH or sepsis. According to our findings and previous studies by others (11, 23), there is now evidence for a higher threshold of ferritin to diagnose secondary HLH in the ICU. In our cohort, highest ferritin levels were seen in HLH patients, followed by septic shock and sepsis patients, surpassing the levels in all other diagnoses. However, despite these encouraging results for identifying HLH, ferritin must always be interpreted in the context of the patient's underlying condition, clinical course,

and additional HLH diagnostic criteria. As argued by Sackett et al (5), ferritin has a rather low positive predictive value, possibly placing patients at risk to overtreatment if HLH is considered but in fact not present. In addition, our data revealed that severe hyperferritinemia is present in multiple other conditions, including tuberculosis, hepatitis, and other viral infections. Nevertheless, ferritin was still highest in HLH compared with all other conditions. These findings have implications for clinical practice. Differential diagnosis of the causes of hyperferritinemia will have to largely rely on the degree of ferritin elevation. The presence of severely elevated ferritin levels exceeding limits seen in tuberculosis, viral infections, renal and hepatic disorders, then warrants further diagnostics to rule out or to confirm a diagnosis of HLH. There is strong evidence that HLH is indeed an underdiagnosed condition (14), that is why we believe that early assessment of ferritin could increase detection rates of HLH, facilitate early treatment, and thereby contribute to improved patient outcome.

Based on our data, a ferritin of 9,083 µg/L was most predictive for HLH. This constitutes a considerably higher threshold than the cutoff of 500 µg/L as proposed in the HLH-2004 criteria. In their cohort of critically ill adult patients, Saeed et al (11) found an optimal cutoff at 3,951 µg/L. Similarly, previous research in our study group had revealed the best prediction accuracy at 3,095 µg/L (14), whereas in another study, in ICU patients (23), ferritin of 1,197 µg/L was correlated best with secondary HLH. In our analyses, even ferritin of 4,006 µg/L showed good prediction accuracy with 95% sensitivity and 83% specificity. However, it has been argued that ferritin alone provides insufficient specificity for diagnosing HLH (24). At a value of ferritin greater than 50,000 µg/L, Schram et al (18) found an only low sensitivity (< 20%) and specificity (17%) for HLH. The authors concluded that in view of the rarity of HLH, more common conditions also associated with hyperferritinemia such as renal and hepatic failure, infections, and malignancies should be considered first. Small sample size and heterogeneity in underlying conditions associated with HLH were potential limitations in previous studies. The studies by Saeed et al (11) and us (14) included nine patients each, most of whom developed septic shock during their clinical course. As our study comprised the currently largest mixed ICU cohort with ferritin available, we could take into account the wide variety of hyperferritinemia-related conditions encountered in the critical care setting and believe that a concentration of 9,083 µg/L for ferritin is a reliable marker, warranting further diagnostics to confirm or exclude HLH. Of note, the threshold of 500 µg/L was established for a pediatric population presenting with primary HLH (10). In this particular patient group, the cutoff of 500 µg/L is well justified because these patients might initially have ferritin levels considerably lower than 9,083 µg/L with a steep increase as HLH progresses. Those patients might remain undetected if the diagnostic threshold is raised without taking the possibility of primary HLH into account. However, in the adult ICU population, ferritin of 500 µg/L has only poor specificity in diagnosing HLH. We, therefore, believe that a markedly higher threshold should be used to avoid confounding HLH with other conditions associated with severe hyperferritinemia in the critical care setting.

Concerns have been raised that secondary HLH remains frequently unrecognized, leading to delayed or no treatment and subsequent high mortality rates, particularly in the critically ill (14, 25–27). The frequency of 1.52% among ICU patients with ferritin of at least 500 µg/L found in our cohort warrants increased awareness of this life-threatening condition. Diagnosis of HLH is often hampered and delayed by its clinical overlap with sepsis or septic shock. As our data demonstrate, ferritin concentrations differ significantly among sepsis, septic shock, and HLH underscoring the role of highly elevated ferritin in recognition of HLH. Therefore, a sepsis-like condition in the presence of refractory fever and unexplained cytopenia demands testing of ferritin levels and further HLH diagnostics.

As one of the HLH-2004 diagnostic criteria, sIL-2R is also an important disease marker in HLH. A value of greater than or equal to 2,400 U/mL has a reported sensitivity and specificity of 93% and 100%, respectively, in pediatric patients (10). Zhang et al (28) reported sIL-2R as an independent marker to predict survival and monitor treatment response. Hayden et al (29) demonstrated an excellent predictive value at 2,515 U/mL with 100% sensitivity and 72.5% specificity in adult non-ICU HLH patients. However, we detected rather unsatisfying sensitivity (66.7%) and specificity (76.6%) at a value of 4,621 U/mL in our large mixed ICU cohort. Therefore, sIL-2R may not be a strong marker of HLH within the ICU population, but this assessment is limited by the relatively small number of sIL-2R testing within this cohort. Of note, at high values exceeding the respective laboratory quantitation standard, sIL-2R and serum ferritin samples require dilution to yield exact results. This is important, as reports of measurements beyond a certain threshold (e.g., > 7,500 U/mL) do not allow for exact clinical evaluation.

We found an increased ferritin concentration to be independently associated with higher mortality. Yet, when trying to determine a cutoff for mortality prediction, discriminatory performance was rather low in ROC analysis. Therefore, ferritin may not be strongly related to in-hospital mortality. Previous research conducted in medical ICU and pediatric critical care patients consistently demonstrated ferritin to be an independent factor for increased mortality (7–9). For HLH patients, Grangé et al (30) showed that ferritin was the only independent predictor of mortality. In line, a decrease in ferritin during therapy was associated with lower mortality rates emphasizing the potential prognostic value of ferritin (31).

Our study has several limitations. First, it is retrospective in nature, limiting data availability to ferritin assessments during hospitalization to the ICU. Because our cohort comprises patients admitted to various ICUs where some might have been more likely than others to have ferritin measurement, there might be a selection bias toward specific disease groups. Second, there is variability in the timing that ferritin levels were obtained as some patients had ferritin measurement at admission, others later during their ICU stay. Third, there is a considerable likelihood that HLH cases in ICU remained undetected based on clinicians' experience. Fourth, as HLH

diagnosis partially relied on expert review, there might be a bias toward HLH diagnosis. Fifth, the overlap of patients between our chosen disease groups might distort results. Finally, our data are derived from an academic medical center, which might limit generalization for a community hospital.

CONCLUSIONS

This is the first study describing clinical characteristics of severe hyperferritinemia in a mixed ICU cohort including 40 HLH cases. Furthermore, it is the largest study of patients with ferritin available in critically ill patients. Ferritin concentrations differed significantly, depending on the underlying condition. Hyperferritinemia was most pronounced in patients with HLH, followed by septic shock, sepsis, and other disease entities. At a cutoff of 9,083 µg/L, prediction accuracy was at 92.5% sensitivity and 91.9% specificity to detect HLH. Ferritin is easy to assess and should therefore be measured in ICU patients with unclear inflammation to increase the detection rate of HLH.

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