2-17-2021

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Recommended Citation
Abou Shaar R, Eby CS, van Dorp S, de Witte T, and Otrock ZK. Increasing ferritin predicts early death in adult hemophagocytic lymphohistiocytosis. Int J Lab Hematol 2021.

Received: 13 November 2020 | Accepted: 29 January 2021

DOI: 10.1111/ijlh.13489

ORIGINAL ARTICLE

ISLH International Journal of Laboratory Hematology WILEY

Increasing ferritin predicts early death in adult hemophagocytic lymphohistiocytosis

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Abstract

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathologic immune activation. Most studies on adult HLH have evaluated prognostic factors for overall survival; factors predicting early mortality have not been sufficiently investigated.

Methods: This was a collaborative study between Henry Ford Hospital and Barnes-Jewish Hospital. We identified all adult HLH patients with at least 2 ferritin levels within 30 days from admission.

Results: One-hundred twenty-four patients were identified. There were 77 males and 47 females; the median age at diagnosis was 48 years. Multivariate analysis showed that age (OR = 11.41; 95% CI:2.71-48.04; $P = .001$), hepatomegaly (OR = 15.68; 95% CI:3.24-75.96; $P = .001$), hyponatremia (OR = 5.94; 95% CI:1.76-20.1; $P = .004$), hypoalbuminemia (OR = 7.47; 95% CI:2.08-26.85; $P = .002$), and increasing ferritin levels (OR = 19.46; 95% CI:4.69-80.71; $P < .001$) were significant predictors of 30-day mortality. Patients with declining ferritin by more than 35% from the ferritin peak were more likely to survive the first 30 days of admission (OR = 4.33; 95% CI:1.04-18.1; $P = .033$). By risk stratifying our cohort, we identified changes in ferritin levels to be the most significant prognostic factor of 30-day mortality among other risk factors. Further investigating the prognostic utility of ferritin showed that increasing ferritin during the 1st week of admission (data available for 44 patients) was the only significant predictor of 30-day mortality.

Conclusions: To the best of our knowledge, this is the first study reporting changes in ferritin to be a predictor for early death in adult HLH. Changes in ferritin might be a useful indicator of adult HLH disease activity and early prognosis.

KEYWORDS

adult, change, early death, ferritin, hemophagocytic lymphohistiocytosis, predictor

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathologic immune activation resulting in hyper-inflammatory response.[1,2] HLH can be either primary (familial) or secondary (acquired). Primary HLH occurs most commonly in infants and young children and is caused by genetic defects in proteins involved in the function of T lymphocytes and natural killer (NK) cells.[3] On the other hand, secondary HLH typically occurs in adults and is often triggered by infections the most recent of which is COVID-19,[4] malignancies,

autoimmune diseases, acquired immune deficiency, as well as immune suppression and hematopoietic stem cell transplantation.[5] In some cases, the initiating cause of HLH is not identified.

The common clinical and laboratory features of HLH are fever, hepatosplenomegaly, cytopenias, hyperferritinemia, and hypertriglyceridemia accompanied with or without hypofibrinogenemia.[6] Hemophagocytosis involving the bone marrow, liver, or any part of the reticuloendothelial system is characteristic, though not specific for HLH.[7] The Histiocyte Society published the first diagnostic guidelines for HLH in 1991[8] and revised them in 2004.[9] Although these criteria were initially applied to pediatric HLH, they are also used to diagnose adult HLH.

HLH can affect patients of all ages. Diagnosis of HLH is challenging for physicians, and it may be delayed. The clinical and laboratory findings in HLH resemble presentations of some of the diseases that trigger the pathologic immune response.[10] Often HLH mimics severe sepsis, multiorgan dysfunction syndrome (MODS), and systemic inflammatory response syndrome (SIRS).[11,12] HLH has a dismal outcome, and fatality rate is high during the first few weeks due to end-organ damage.[13] Most studies of adult HLH have evaluated prognostic factors for overall survival; factors predicting early mortality have not been extensively investigated. We retrospectively studied 124 patients to determine the possible risk factors of early death in adult HLH. We hypothesized that changes in ferritin are associated with risk of early mortality in adult HLH.

2 | MATERIAL AND METHODS

2.1 | Patients

This was a collaborative study between Henry Ford Hospital (Detroit, Michigan) and Barnes-Jewish Hospital (St. Louis, Missouri). The Institutional Review Boards (IRB) of both institutions approved these retrospective chart review studies and waived the requirement for written informed consent. All adult patients (≥18 years) with a diagnosis of HLH were identified at Barnes-Jewish Hospital from October 2003 through June 2017, and at Henry Ford Hospital from April 2010 through December 2019. A diagnosis of HLH was established based on the 2004 Histiocyte Society Criteria (HLH-2004) which requires five of the following eight criteria: (a) fever ≥ 38.5°C; (b) splenomegaly; (c) cytopenias of two or three cell lines: absolute neutrophil count (ANC) $<1 \times 10^9$/L, hemoglobin < 9 g/dL, platelet count $< 100\times10^9$/L; (d) serum triglycerides ≥ 265 mg/dL or fibrinogen ≤ 150 mg/dL; (e) serum ferritin ≥ 500 mcg/L; (f) soluble IL-2 receptor (soluble CD25) ≥2400 U/mL; (g) low/absent NK cell activity; and (h) tissue histology showing hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver.[9] In addition, we included in the analysis only patients who had at least two ferritin levels within 30 days of admission. Admission ferritin was the initial ferritin, and peak ferritin was the highest ferritin within 30 days after admission. We classified ferritin changes during admission as increasing (peak ferritin being the last ferritin value) or decreasing (ferritin values decreasing after peak ferritin). Patients who were clinically managed as HLH, but did not meet the HLH-2004 criteria, were not included in the study. We determined the most likely trigger of secondary HLH (malignancy, infection, autoimmune, and idiopathic) based on treating physician's assessment or evidence we retrieved from the medical record.

2.2 | Data collection

We reviewed all available electronic medical records including patients' charts, laboratory, and pathology reports. We collected demographic information, medical history and underlying diseases, clinical presentation, and laboratory results, treatments, and survival. We screened medical records for information on immunosuppression, organ damage including hepatomegaly, transaminitis (aspartate transaminase (AST) and/or alanine transaminase (ALT) levels above the normal reference range), hypoalbuminemia, renal insufficiency (serum creatinine level above the normal reference range), coagulopathy (defined as prolonged prothrombin time (PT) and/or prolonged activated partial thromboplastin time (aPTT)), and hypofibrinogenemia (≤150 mg/dL). Analyses of laboratory values were based on reference ranges at each institution.

2.3 | Statistical methods

Results were presented as median plus range, or percentages as indicated. In the univariate analysis, the independent two-sample *t* test for continuous data and Pearson's chi-square test or Fisher's exact test for categorical data were used to determine the significance and odds ratio (OR) for the independent clinical and laboratory variables as related to 30-day mortality. Thirty-day mortality was defined as death from any cause within 30 days of admission. Ferritin values within 30 days of admission were used to determine whether the ferritin trend was decreasing or increasing in relation to peak ferritin. A multivariate analysis was performed using logistic regression to identify the risk factors for early mortality. A backward stepwise (Wald) selection model was performed, with significance level for removal from the model set at 0.1. The method of Kaplan-Meier was used to plot survival curves and estimate survival probabilities. Log-rank test was used to compare the survival curves between groups. All tests of significance were two-sided, and a *P* value of <.05 was regarded as significant. All statistical analyses were performed using SPSS software, version 22 (SPSS Inc).

3 | RESULTS

3.1 | Clinical characteristics and laboratory tests

We included 124 adult HLH patients in our analysis who fulfilled the inclusion criteria (88 patients from Barnes-Jewish Hospital and 36

patients from Henry Ford Hospital). The selection of patients for analysis was based on the algorithm shown in Figure S1. There were 77 males and 47 females; the median age at diagnosis was 48 years (range: 18-84 years). Ethnicity was distributed as follows: Caucasian (n = 89, 71.8%), African American (n = 29, 23.4%), and Asian (n = 6, 4.8%). The initial characteristics of patients are summarized in Table 1.

The likely causes or triggers of HLH in our patients were as follows: 45 (36.3%) infections, 43 (34.7%) malignancies, 9 (7.2%) autoimmune disorders, 1 (0.8%) primary immunodeficiency, 2 (1.6%) postsolid organ transplantation, and 24 (19.4%) idiopathic (Table 2). In the 45 patients with infectious diseases, viral infections were the most common cause with 9 (20%) EBV cases and 6 (13.3%) HIV cases. Bacterial and fungal infections were identified in 12 and 6 patients, respectively. Among the malignancy-associated HLH cases, B-cell lymphoma followed by T-cell lymphoma and Hodgkin lymphoma were the most common diagnoses. Systemic lupus erythematosus (SLE) was the most common diagnosis among autoimmune-associated HLH cases.

Fever was present in 119 (95.2%) patients with a median maximum temperature of 39.3°C (range: 37.2°C-42.2°C). Splenomegaly and hepatomegaly occurred in 89 (71.8%) and 30 (24.2%) patients, respectively. Most patients were anemic (90.3%) and thrombocytopenic (93.5%) at presentation with a median hemoglobin of 8 g/dL (range: 4.1 g/dL-12.6 g/dL) and median platelet count of 43×10^9/L (range: 6×10^9/L-432×10^9/L). Neutropenia (ANC < 0.5×10^9/L) was identified in 41 (33.1%) patients with a median ANC of 2.1×10^9/L (range: 0×10^9/L-52.6×10^9/L). Nearly all patients had an elevated serum lactate dehydrogenase (LDH) (N = 111/119; 93.3%), and a majority had increased transaminases, triglycerides, and total bilirubin:

TABLE 1 Patients' initial characteristics

Variable	Median (Range)
Age, years	48 (18-84)
Gender, no. of patients	77 males, 47 females
Ethnicity, no. of patients (%)	Caucasian 89 (71.8)
	African American 29 (23.4)
	Asian 6 (4.8)
Splenomegaly, no. of patients (%)	89 (71.8%)
Hepatomegaly, no. of patients (%)	30 (24.2%)
White blood cell count, $\times 10^9$/L	3.85 (0.1-57.1)
Absolute neutrophil count, $\times 10^9$/L	2.1 (0-52.6)
Hemoglobin, g/dL	8 (4.1-12.6)
Platelet count, $\times 10^9$/L	43 (6-432)
Admission ferritin, mcg/L	12 308 (932-684 000)
Peak ferritin, mcg/L	25 736 (1412-684 000)
Fibrinogen, mg/dL	186.5 (26-818)
Triglycerides, mg/dL	374 (63-1984)
Hemophagocytosis, no. of patients (%)	83/111 (74.8%)
AST, U/L	169.5 (14-10 056)
ALT, U/L	10 (100-9340)
LDH, U/L	849 (15-16 020)
aPTT (seconds)	42 (15-200)
PT (seconds)	17.1 (10.1-58.3)
Sodium, mmol/L	132 (118-155)
Albumin, g/dL	2.4 (1.1-4.3)
Total bilirubin, mg/dL	1.5 (0.2-63.3)

Note: Abbreviations: ALT, Alanine transaminase; aPTT, activated partial thromboplastin time; AST, Aspartate transaminase; LDH, lactate dehydrogenase; no., number; PT, prothrombin time.

TABLE 2 Underlying disorders associated with adult HLH patients (n = 124)

Cause	No. of patients
Infection, n = 45 (36.3%)	
EBV	9
HIV	6
Hepatitis C virus	2
CMV	1
Other viruses	9
Bacterial	12
Fungal	
Histoplasmosis	3
Candidemia	1
Coccidiomycosis	1
Aspergillosis	1
Malignancy, n = 43 (34.7%)	
B-cell lymphoma	15
T-cell lymphoma	14
Hodgkin lymphoma	6
Myelodysplastic syndrome	4
Acute myelogenous leukemia	1
Acute lymphoblastic leukemia	1
Metastatic prostate cancer	1
HLH occurring during chemotherapy	1
Autoimmune, n = 9 (7.2%)	
Systemic lupus erythematosus	5
Adult-onset Still's disease	3
Juvenile rheumatoid arthritis	1
Primary immunodeficiency, n = 1	
DiGeorge syndrome	1
Post solid organ transplantation, n = 2	
Liver transplant	1
Kidney and pancreas transplant	1
Idiopathic, n = 24 (19.4%)	24

107 (86.3%), 91 (N = 91/121; 75.2%), and 75 (60.5%), respectively. Decreased fibrinogen was confirmed in 49 patients (N = 49/116; 42.2%). Prolonged PT and/or aPTT occurred in 110 (88.7%) patients. Eighty-two (66.1%) patients were hyponatremic.

There was histologic evidence of hemophagocytosis in 83/111 (74.8%) patients' bone marrow, lymph node, liver, or spleen tissues. Seventy-two out of 104 (69.2%) bone marrows showed hemophagocytosis. In both institutions, soluble Il-2 receptor and NK cell activity assays were sent to reference laboratories. Soluble Il-2 receptor was increased in 86.1% (N = 56/65) of patients. NK cell activity was decreased in 46.1% (N = 6/13) of cases, and it failed in another 4 cases. Genetic testing for primary HLH was negative in all 11 tested patients.

3.2 | Ferritin trends

On admission, ferritin was greater than 500 mcg/L in all patients with a median ferritin of 12 308 mcg/L (range: 932 mcg/L-684 000 mcg/L). The median peak ferritin was 25 736 mcg/L (range: 1412 mcg/L-684 000 mcg/L); the number of patients having peak ferritin >10 000 mcg/L, >25 000 mcg/L, >50 000 mcg/L, and >100 000 mcg/L was 99 (79.8%), 63 (50.8%), 33 (26.6%), and 14 (11.3%) patients, respectively. A decreasing ferritin trend occurred in 85 (68.5%) patients during the first 30 days of admission.

3.3 | Treatment

Medical management varied based on the underlying trigger for HLH and physicians' decisions. Patients with infection-associated HLH were treated with antiviral, antibiotic, and antifungal therapies, with the addition of steroids in some cases. Among the 9 EBV-associated HLH, 4 patients were treated with etoposide-based regimens including 2 patients treated with HLH-2004 protocol; the remaining patients received antiviral therapy (N = 2), supportive measures (N = 2), and steroids (N = 1).

Among the 35 patients with lymphoid malignancies, 10 patients received etoposide-based chemotherapy regimens with 2 patients receiving rituximab. Ten patients were treated with R-CHOP or CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab). One patient received maintenance therapy with methotrexate, one was treated with cyclophosphamide, two received rituximab, and one patient was treated with cyclophosphamide and rituximab. Eight patients were treated with steroids, and two patients received supportive care.

Nine patients with autoimmune-associated HLH received steroids alone (N = 6) or in combination with cyclosporine (N = 3). Idiopathic HLH cases were treated with various combinations of steroids (N = 6), etoposide (N = 10), cyclosporine (N = 2), IVIG (N = 2), or supportively (N = 4).

3.4 | Outcome, 30-day mortality, and survival

Median duration of hospitalization was 20 days (range: 1-89 days). The 30-day mortality rate was 27.4% (N = 34/124); death was attributed to sepsis and multiorgan failure in 24 patients, malignancy in 6, bleeding in 2, liver failure in 1, and unknown in 1. The median overall survival (OS) of the entire cohort was 2.8 months (95% CI:0-6.12), with a 1-year OS of 39.2% (Figure S2).

In the univariate analysis, when comparing major clinical and laboratory parameters, we found that age (≥50 years), thrombocytopenia (platelet count $< 40\times10^9$/L), hepatomegaly, hyponatremia (sodium < 132 mmol/L), hypoalbuminemia (albumin < 2.4 g/dL), and increasing ferritin were predictors of 30-day mortality (Table 3). Multivariate analysis showed that age (OR = 11.41; 95% CI:2.71-48.04; $P = .001$), hepatomegaly (OR = 15.68; 95% CI:3.24-75.96; $P = .001$), hyponatremia (OR = 5.94; 95% CI:1.76-20.1; $P = .004$), hypoalbuminemia (OR = 7.47; 95% CI:2.08-26.85; $P = .002$), and increasing ferritin (OR = 19.46; 95% CI:4.69-80.71; $P < .001$) remained significant predictors of 30-day mortality (Table 3; Figure 1). In addition, patients with declining ferritin by more than 35% from the ferritin peak were more likely to survive the first 30 days from admission (OR = 4.33; 95% CI:1.04-18.1; $P = .033$). Patients with increasing ferritin of more than 35% were more likely to die (OR = 5.67; 95% CI:1.02-31.54; $P = .035$).

Increasing ferritin appeared to be the most significant prognostic factor among other factors obtained at the level of multivariate analysis. In order to better elucidate the contribution of ferritin as a predictor of early mortality, we stratified our cohort into three risk groups based on the number of risk factors obtained at the multivariate analysis: low risk defined as patients with no risk factors; intermediate risk defined as patients with one or more risk factors excluding increasing ferritin; and high risk defined as patients with increasing ferritin with or without other risk factors. Table 4 summarizes the risk groups' stratification with their 30-day survival. Figure 2 shows the Kaplan-Meier survival curves of the three risk groups. Compared to intermediate-risk group patients, patients in the high-risk group had greater than 4 times increased risk of early death (OR = 4.37; 95% CI:1.85-10.31; $P = .001$).

We investigated whether changes in ferritin occurring early during admission were predictive of early mortality. We identified 44 patients who had multiple ferritin measurements (at least two) during the 1st week of hospital admission. Multivariate analysis showed that increasing ferritin was the only significant predictor of 30-day mortality (Table S1).

Subgroup analysis of malignancy-associated HLH (N = 43) confirmed the significance of increasing ferritin as a predictor of 30-day mortality (OR = 16.07; 95% CI:2.8-92.16; $P = .001$). However, neither initial nor peak ferritin levels correlated with 30-day mortality.

For nonmalignancy-associated HLH (N = 81), a peak ferritin > 50 000 mcg/L was associated with 30-day mortality (OR = 3.4; 95% CI:1.11-10.45; $P = .028$). Increasing ferritin correlated with 30-day mortality (OR = 4.25; 95% CI:1.42-12.76; $P = .007$).

TABLE 3 Univariate and multivariate analysis of predictors of early mortality (30-day) in adult HLH . Significant p values are shown in bold.

Parameters	Survivors	Nonsurvivors	OR (95% CI)	*P* value
Univariate analysis				
Age				
≥50 years	36	24	3.6 (1.54-8.42)	**.002**
<50 years	54	10		
Gender				
Male	55	22	0.86 (0.38-1.95)	.71
Female	35	12		
Ethnicity				
Caucasian	67	28	0.62 (0.23-1.70)	.35
Other	23	6		
Immunosuppression				
Yes	40	13	1.29 (0.58-2.90)	.53
No	50	21		
Neutropenia				
Yes	32	9	1.53 (0.64-3.68)	.34
No	58	25		
Anemia				
Yes	81	31	0.87 (0.22-3.43)	1.0
No	9	3		
Thrombocytopenia (Plt < 40×10^9/L)				
Yes	33	22	3.17 (1.39-7.22)	**.005**
No	57	12		
Splenomegaly				
Yes	62	27	0.57 (0.22-1.48)	.24
No	28	7		
Hepatomegaly				
Yes	17	13	2.66 (1.11-6.34)	**.025**
No	73	21		
Renal insufficiency				
Yes	41	21	0.52 (0.23-1.16)	.11
No	49	3		
Hyponatremia (Na < 132 mmol/L)				
Yes	37	22	2.63 (1.16-5.96)	**.019**
No	53	12		
Hemophagocytosis (N = 111)				
Yes	62	21	0.98 (0.37-2.64)	.98
No	21	7		
Hypertriglyceridemia (N = 121)				
Yes	66	26	0.81 (0.31-2.12)	.66
No	22	7		
Hypofibrinogenemia (N = 116)				
Yes	33	16	0.65 (0.28-1.47)	.30
No	51	16		
Elevated sIL2R (N = 65)				
Yes	43	13	0.41 (0.05-3.61)	.67
No	8	1		
Admission ferritin (>10 000 mcg/L)				
Yes	51	17	0.76 (0.35-1.69)	.51
No	39	17		
Peak ferritin (>25 000 mcg/L)				
Yes	47	17	0.92 (0.42-2.01)	.84
No	43	17		
Ferritin change (increase)				
Yes	19	20	5.34 (2.28-14.49)	**<.001**
No	71	14		
Coagulopathy (prolonged PT and/or aPTT)				
Yes	79	31	0.70 (0.18-2.66)	.76
No	11	3		
Transaminitis (elevated AST and/or ALT)				
Yes	78	29	1.12 (0.36-3.46)	.84
No	12	5		
Hypoalbuminemia (albumin < 2.4 g/dL)				
Yes	38	22	2.51 (1.11-5.69)	**.025**
No	52	12		
Hyperbilirubinemia (total bilirubin > 1.2 mg/dL)				
Yes	55	20	1.1 (0.49-2.46)	.82
No	35	14		
Elevated LDH (N = 119)				
Yes	80	31	0.86 (0.16-4.49)	1
No	6	2		
Etoposide-based treatment				
Yes	23	9	0.95 (0.39-2.34)	.92
No	67	25		
Associated malignancy				
Yes	27	16	2.07 (0.92-4.66)	.075
No	63	18		
Multivariate analysis				
Age (≥50 years)			11.41 (2.71-48.04)	**.001**
Hepatomegaly			15.68 (3.24-75.96)	**.001**
Hyponatremia (Na < 132 mmol/L)			5.94 (1.76-20.1)	**.004**
Hypoalbuminemia (albumin < 2.4 g/dL)			7.47 (2.08-26.85)	**.002**
Ferritin change (increase)			19.46 (4.69-80.71)	**<.001**

(Continues)

Note: Abbreviations: ALT, Alanine transaminase; aPTT, activated partial thromboplastin time; AST, Aspartate transaminase; LDH, lactate dehydrogenase; Na, sodium; Plt, platelet count; PT, prothrombin time; sIL2R, soluble IL-2 receptor.

We performed the same analysis now evaluating the predictors of 100-day mortality. Multivariate analysis showed that age, hyponatremia, and increasing ferritin were significant predictors of 100-day mortality (Table S2). In addition, changes in ferritin remained the most significant prognostic factor using the risk group stratification approach (Table S3). Figure S3 shows the survival curves (100-day survival) of the three risk groups.

4 | DISCUSSION

In this study, we explored a large number of prognostic factors using multivariate analysis focusing on early mortality as an outcome. The 30-day mortality rate in our cohort was 27.4%. Our results showed that age (≥50 years), hepatomegaly, hyponatremia (sodium < 132 mmol/L), hypoalbuminemia (albumin < 2.4 g/dL), and increasing ferritin were associated with 30-day mortality. Parikh and colleagues found that malignancy and hypoalbuminemia were associated with poor overall survival.[14] In another study by Aulagnon et al, acute kidney injury and hematologic malignancies have been associated with 6-month mortality.[15] Another report highlighting infection-associated HLH identified age > 50 years, persistent fever of 3-day duration, and presence of disseminated intravascular coagulation as significant indicators of mortality.[16] Arca et al recognized increasing age, decreasing platelet count, underlying lymphoma, and no etoposide in treatment as poor prognostic risks for early death in a cohort of 162 adult HLH patients.[17] A recent study by Zhao and colleagues identified age ≥ 54 years, platelet count ≤ 39.5 × 10^9/L, aPTT ≥ 54 sec, triglycerides ≥ 3.23 mmol/L, LDH ≥ 1300 U/L, and malignancy as predictors of 30-day mortality in adult HLH.[18] Age is one of the predictors we have identified in our study, and thrombocytopenia lost significance at the multivariate level.

Similar to observations by other investigators, ferritin values in our study were far above the 500 mcg/L cutoff set by the

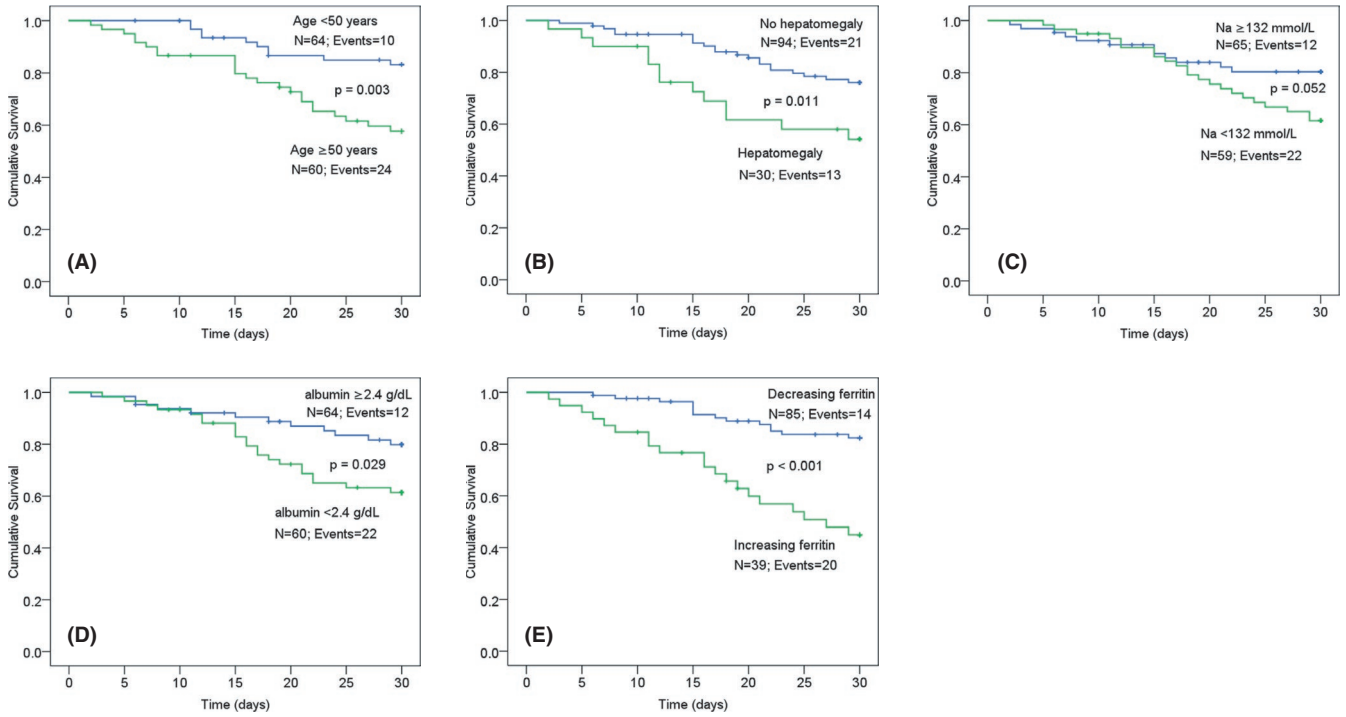

FIGURE 1 Survival curves of HLH patients with the significant prognostic risk factors of early death. (A) Age; (B) Hepatomegaly; (C) Hyponatremia; (D) Hypoalbuminemia; (E) Ferritin change [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Summary of the three risk groups with their 30-day survival and median 30-day survival

Risk group[a]	Number of patients	Number of events	30-day survival	Median 30-day survival
Low risk	13	0	100%	Not reached
Intermediate risk	72	14	79.2%	Not reached
High risk	39	20	44.9%	27 days

Note: Low risk: zero risk factors; Intermediate risk: 1 or more risk factors excluding ferritin change; High risk: includes ferritin change.

[a]Parameters which were significant in the multivariate analysis (ie, age, hepatomegaly, hyponatremia, hypoalbuminemia, and ferritin change) were taken as risk factors.

HLH-2004 diagnostic criteria. Mild to moderate ferritin elevations are associated with many conditions, including infections, inflammatory disorders, and cancer. Many investigators have proposed higher ferritin cutoffs with varying specificities for HLH. Our group has shown that elevated ferritin (>10 000 mcg/L) is also not specific for pediatric or adult HLH, although its specificity increases with higher cutoffs.[19] This ferritin cutoff was also nonspecific in diagnosing adult HLH in other studies.[20,21] Other investigators proposed ferritin levels above 30 000 μg/L to be highly specific for HLH.[22] In addition, investigations of the prognostic value of ferritin have produced inconsistent results. Hyperferritinemia (>50 000 mcg/L) correlated with 30-day mortality in malignancy-associated HLH.[23] Yoon and colleagues identified elevated ferritin > 20 000 mcg/L to be associated with poor survival outcomes.[24] In line with these thoughts, a recent systematic review by Sarangi and colleagues highlighted the controversies of ferritin as a diagnostic and prognostic marker in HLH.[25] The authors concluded that the available diagnostic ferritin cutoff value of 500 mcg/L was low and clinically not relevant; thus, a revision of the existing guidelines considering higher ferritin cutoff values is suggested. Compared to pediatric HLH, higher ferritin cutoff values (>2000 mcg/L) were predictive of adult HLH diagnosis. Some studies on adult HLH have shown correlation between post-treatment ferritin values (sometimes decline in ferritin level) with overall survival; however, these findings were not elucidated by other studies.[25]

Our findings have added ferritin change as a prognostic factor in adult HLH. We have found that increasing ferritin during admission correlated with early death (OR = 19.46; 95% CI:4.69-80.71; $P < .001$). In addition, patients with declining ferritin (at least 35% decrease in ferritin) were more likely to survive while patients with increasing ferritins (at least 35% increase in ferritin) were more likely to die. Additionally, we have shown through logistic regression and risk stratification that ferritin change was the most prognostic factor of early death among the other identified risk factors. Therefore, frequent ferritin measurements may be useful in predicting outcomes and in guiding physicians in risk stratifying adult HLH patients. Other investigators have established ferritin measurements as a method to evaluate response to therapy in children. Lin and colleagues followed ferritin levels in 48 pediatric HLH patients; they found that a rapid decline of ferritin levels in the first 3 weeks following therapy was associated with decreased mortality.[26]

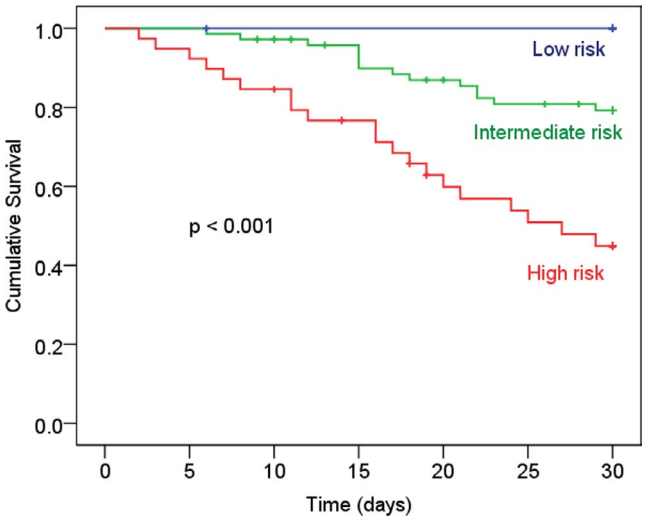

FIGURE 2 Kaplan-Meier survival curves of the three risk groups showing 30-day survival [Colour figure can be viewed at wileyonlinelibrary.com]

4.1 | Study limitations

This study has several strengths, including the large number of adult HLH patients with a diverse spectrum of HLH triggers. The data were collected from two medical centers over a long period. Our study also has some limitations. This was a retrospective study and dependent on case selection criteria and medical record diagnosis coding. The possibility of data recording bias or inaccurate diagnoses cannot be excluded. While we might have not identified some HLH diagnoses, we minimized this risk by using multiple databases in our search methodology to identify HLH cases in both institutions. Patients might have been underdiagnosed if some of the criteria for HLH were not routinely checked especially the specialized referral tests (ie, soluble IL-2 receptor and NK cell activity). Nevertheless, this study captured a large number of adult HLH patients and was able to identify new prognostic factors for early death.

Second, we used the HLH-2004 diagnostic criteria to define adult HLH. However, these criteria may be too strict for adults with secondary HLH and may not include some of the common clinical and laboratory findings present in these patients. For example, transaminitis, hypoalbuminemia, and coagulopathy were observed in most of our patients, yet these findings are not included in the diagnostic criteria. There remains a need to refine adult HLH diagnostic criteria by validating clinical and laboratory findings independently in a large adult HLH cohort or registry.

Third, patients' management may have changed over time and between the two institutions, which could have affected our results.

5 | CONCLUSIONS

Physicians are diagnosing HLH with increasing frequency in adults. Early mortality of adult HLH still represents a major challenge for clinicians. Any delay in diagnosis or treatment initiation could be associated with increased mortality. It would be useful to identify subjects at high risk for early death and therefore consider early or aggressive therapy. We examined the clinical and laboratory characteristics of 124 patients with adult HLH to identify risks of early death. Our results showed that age, hepatomegaly, hyponatremia, hypoalbuminemia, and increasing ferritin were associated with

30-day mortality. To the best of our knowledge, this is the first study reporting ferritin change to be a prognostic factor for early death and, more importantly, to contribute the most to early death among other identified risk factors. Ferritin is a cost-effective and readily available biomarker in most clinical laboratories. Prospective studies will be necessary to determine whether frequent measurement of ferritin is an important predictor adult HLH disease activity and early prognosis.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

RA captured eligible cases and collected data. CE treated patients and reviewed the paper. SV designed the research study and reviewed the paper. TD designed the research study and reviewed the paper. ZO designed the research study, captured eligible cases, analyzed data, and wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Abou Shaar R, Eby CS, van Dorp S, de Witte T, Otrock ZK. Increasing ferritin predicts early death in adult hemophagocytic lymphohistiocytosis. *Int J Lab Hematol*. 2021;00:1–8. https://doi.org/10.1111/ijlh.13489