OBSERVATIONAL STUDY

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Hemophagocytic Lymphohistiocytosis in the Medical ICU: A Single-Institution Cohort Study on Acute Liver Failure and Mortality

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OBJECTIVES: Hemophagocytic lymphohistiocytosis is a life-threatening hyperinflammatory disorder that is associated with high morbidity and mortality in the ICU. It has also been associated with acute liver failure.

DESIGN: Retrospective observational study.

SETTING: Tertiary-care medical ICU.

PATIENTS: Thirty-one patients critically ill with hemophagocytic lymphohistiocytosis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We performed a comprehensive review of critically ill hemophagocytic lymphohistiocytosis patients admitted to a tertiary-care medical ICU from January 2012 to December 2018. Most patients presented with constitutional symptoms and elevated liver enzymes and thrombocytopenia were common upon hospital admission. ICU admission laboratory and clinical variables were used to calculate Acute Physiology and Chronic Health Evaluation II, hemophagocytic syndrome diagnostic score, and model for end-stage liver disease. Mean age of the cohort was 48.1 years, and 45% were male. The mortality rate was 65% at 28 days and 77% at 1 year. About 28-day survivors were younger, had lower mean Acute Physiology and Chronic Health Evaluation II score (16.5 vs 23.0; $p = 0.004$), and higher mean hemophagocytic syndrome diagnostic score (249.1 vs 226.0; $p = 0.032$) compared with nonsurvivors. Survivors were less likely to receive mechanical ventilation, renal replacement therapy, or vasopressor support and were more likely to receive chemotherapy for hemophagocytic lymphohistiocytosis. In this ICU cohort, 29% were diagnosed with acute liver failure, of whom only 22% developed acute liver failure early during their hospital stay. Acute liver failure was associated with a higher model for end-stage liver disease score upon hospital admission. Available histology in those that developed acute liver failure showed massive hepatic necrosis, or histiocytic or lymphocytic infiltrates.

CONCLUSIONS: Patients admitted to the ICU with hemophagocytic lymphohistiocytosis have a high mortality. Those who survived had lower Acute Physiology and Chronic Health Evaluation scores, had higher hemophagocytic syndrome diagnostic scores, are more likely to receive hemophagocytic lymphohistiocytosis specific chemotherapy, and are less likely to have organ failure. Hemophagocytic lymphohistiocytosis can be associated with acute liver failure especially when model for end-stage liver disease score is elevated upon admission.

KEY WORDS: hemophagocytic lymphohistiocytosis; hemophagocytic syndrome; hemophagocytic syndrome diagnostic score; intensive care unit mortality; liver failure; model for end-stage liver disease

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Hemophagocytic syndrome, also referred to as hemophagocytic lymphohistiocytosis (HLH), is a life-threatening hyperinflammatory disorder first described in 1939 as histiocytic medullary reticulosis. Primary HLH is a familial, X-linked disorder, resulting in uncontrolled activation in T-cells, macrophages, and inflammatory cytokines (1). Adults most commonly present with secondary HLH, which can develop in those with infection, malignancies, or autoimmune diseases (2, 3). Described clinical presentations of HLH vary and include fever of unknown origin, sepsis like disease, vasculitis, neurologic abnormalities, and acute hepatitis with acute liver failure (ALF) (4, 5). Because HLH lacks unique clinical, pathologic, and laboratory features, its diagnosis has been largely based on the HLH-2004 criteria, which weights clinical, laboratory, and biopsy histopathologic criteria observed with HLH (6). More recently, other differentially weighted diagnostic tools have been proposed for diagnosis, including the hemophagocytic syndrome diagnostic score (HScore), which also includes clinical, laboratory, and pathologic data and omits laboratory values not commonly available, such as soluble interleukin-2 (sIL-2) receptor concentration and natural killer (NK) cell activity (3, 7). Although increasingly recognized in the critically ill adult patient population, some have suggested that HLH is an underdiagnosed cause of morbidity and mortality in the ICU (8). HLH may be underrecognized due to nonspecific symptoms, often attributed to sepsis. HLH associated with critical illness is thought to carry a high inhospital mortality rate 60–68%, but timely diagnosis and treatment are believed to improve mortality (9, 10).

Elevated liver enzymes and hyperbilirubinemia are common in HLH (5), but ALF is reported to be as low as 1% (10). However, the true burden of HLH-associated ALF is not well characterized due to HLH underdiagnosis and the sparsity of larger case studies on HLH. The prevalence of ALF in HLH, and the clinical characteristics and prognosis of those who develop ALF is not known. Additionally, larger studies are needed to characterize further critically ill patients, investigate the pathophysiology of ALF in HLH, and validate prognostic factors and scoring systems such as HScore in this population.

The aim of this study is to determine the prevalence of ALF in HLH patients and correlate admission model for end-stage liver disease (MELD) score, HScore, and other laboratory findings on the development of ALF in HLH patients. We also highlight patient outcomes, including mortality, through a retrospective analysis using a large cohort of adult HLH patients cared for in a tertiary-care medical ICU. We hypothesized that HLH would be associated with a high mortality rate and a higher prevalence of liver failure than what previously reported.

MATERIALS AND METHODS

Patient Selection

A retrospective chart review was used to identify patients diagnosed with HLH admitted to the medical ICU (MICU) at Indiana University Hospital, a large tertiary-care center in Indianapolis, IN, between January 2012 and December 2018. Patients with HLH were identified using billing codes D76.1 (*International Classification of Diseases* [ICD], 10th Revision) and 288.4 (ICD-9th Revision). Of these, 33 patients fulfilled HLH-2004 criteria (11) and two patients were further confirmed by autopsy findings (autopsy was performed due to the lack of clear cause of death and under family request). Patients younger than 18 years, without at least 1 year of follow-up or who did not meet HLH-2004 criteria, were excluded from the study. Patients missing laboratory values necessary for this calculation (two patients) were excluded from analysis. A total of 31 patients were included in this study. This study was approved by the Indiana University Institutional Review Board (protocol number 1702323811).

Data Collection and Outcomes

Clinical data, including patient demographics, past medical history, substance use, medications, clinical symptoms, laboratory data, and follow-up, were obtained from review of the electronic medical record. HLH was defined by meeting five out of eight HLH-2004 criteria: fever, splenomegaly, cytopenias affecting greater than or equal to two peripheral blood lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK cell activity, ferritin greater than or equal to 500 mg/L, and soluble CD25 greater than or equal to 2,400 U/mL (6). All laboratory and pathologic assessments were performed at Indiana University except sIL-2 and NK functions, which were the send-out studies to Cincinnati Children Hospital.

The date of diagnosis was defined as the first mention of HLH diagnosis or initiation of treatment for suspected disease. Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated using data from the time of admission to the MICU (12). ALF was defined as an episode of acute hepatitis with total bilirubin greater than 3 mg/dL, coagulopathy (international normalized ratio [INR] > 1.5), and hepatic encephalopathy in a patient with a previously normal INR without preexisting cirrhosis (13). HScore was calculated from data collected during MICU admission (7). MELD score was calculated using five clinical and laboratory variables upon admission to our hospital (14).

The primary outcome was 28-day mortality after diagnosis in HLH patients and those HLH patients with ALF. Secondary outcomes included 1-year mortality, HScore, time to diagnosis from the start of symptoms, presence of ALF, need for mechanical ventilation, need for continuous renal replacement therapy, and need for vasopressor medications.

Statistical Analysis

Mean and SD were used to describe normally distributed continuous variables, whereas categorical variables were displayed as a percentage. Median and interquartile range were determined for nonnormally distributed continuous variables. Analysis of variance was used to compare different continuous variables between different groups. Chi-square or Fisher exact test (if expected values were low) was used to compare categorical data. Results were considered to have statistical significance for two-sided p values less than 0.05.

RESULTS

A total of 31 patients were included in the final analysis. The median age of the cohort was 52 years (range, 19–84 yr), with 55% female. Demographics, clinical presentation, and laboratory data of the cohort are described in **Table 1**. The median time between symptom/illness onset and diagnosis was 21 days (range, 2–224 d). The most common symptoms at presentation were constitutional symptoms (fever, fatigue, and malaise) in 71% of the patients followed by gastrointestinal symptoms (32%), rash and jaundice (16% each), encephalopathy (6%), and chest pain (3%). Patients commonly presented with thrombocytopenia in 84% of patients and elevation of liver enzymes, including aspartate transaminase (AST) in 77%, alanine transaminase (ALT) in 52%, alkaline phosphatase in 61%, and total bilirubin in 77%. As expected, the mean serum ferritin (29,533 ± 34,131 ng/mL) and sIL-2 receptor concentrations (19,956 ± 22,916 u/mL) were elevated in these patients. Mean HScore was 234.5 ± 28.3 (range, 165–274). The mortality rate of the cohort was 65% at 28 days and 77% at 1 year. Medical conditions triggering HLH, along with their prevalence and mortality, are described in **Table 2**. The most common cause of HLH was infection (45%), followed by malignancy (35%), the majority of which were hematologic malignancies (32% of all HLH cases), and finally autoimmune disease (5%) of the patients. There was no clear etiology identified in 16% of the cohort.

Factors Characterizing HLH Survival at 28 Days From Diagnosis

Comparisons between the HLH patients who were alive or dead at 28 days are presented in **Table 3**. Compared with nonsurvivors, HLH survivors were on average younger than nonsurvivors (38.1 vs 53.6 yr; p =0.035), had lower mean APACHE II score (16.5 vs 23.0; p = 0.004), and had a higher mean HScore (249.1 vs 226.0; p = 0.032). HLH survivors were less likely to receive mechanical ventilation (27.3% vs 90%; p = 0.001), had fewer vasopressor needs (45.5% vs 95.0%; p = 0.004), and were less likely to receive renal replacement therapy (18.2% vs 65.0%; p = 0.023). HLH survivors at 28 days had a lower prevalence of ALF than those who died, but this trend did not reach statistical significance (9.1% vs 40.0%; p = 0.106). Although the average duration between symptom onset and diagnosis appeared to be shorter in the survivors' group, the difference was not statistically significant (5.3 vs 6.5 wk; p = 0.687). Finally, those who survived were more likely to be treated with chemotherapy as part of their HLH directed therapy (81.8% vs 35.0%; p = 0.023).

Table 4 shows the individual characteristics of patients with liver failure. ALF was diagnosed in nine HLH patents (29%), of whom only two developed ALF early during their hospital stay. All patients who were diagnosed of ALF died within 1 year of HLH diagnosis, and the majority (89%) died within 28 days. Liver biopsy was performed in 44% (four of nine) patients, as clinically indicated (**Table 5**). Findings on liver histopathology included massive hepatic necrosis

TABLE 1.
Characteristics of Adults Diagnosed With Hemophagocytic Lymphohistiocytosis During Medical ICU Admission

Characteristics	Adults With Hemophagocytic Lymphohistiocytosis (*n* = 31)
Gender, *n* (%)	
Male	14 (45)
Age group, yr, *n* (%)	
18–39	12
40–59	9
60–79	8
> 80	2
Symptoms, *n* (%)	
Constitutional (fever, malaise, and fatigue)	22 (71.0)
Gastrointestinal (nausea, vomiting, and abdominal pain)	10 (32.3)
Rash	5 (16.1)
Jaundice	5 (16.1)
Cough	5 (16.1)
Encephalopathy	2 (6.5)
Chest pain	1 (3.2)
Time (d) from symptoms onset to diagnosis, median (interquartile range, range)	21.0 (44.5, 2–224)
Acute Physiology and Chronic Health Evaluation II, mean ± sd (median, range)	20.6 ± 6.3 (6–32)
Admission laboratory values, mean ± SD (range)	
Platelets (1,000/mm^3)	110.1 ± 123.8 (8–528)
Hemoglobin (gm/dL)	10.4 ± 2.4 (6–15.6)
WBC (1,000/mm^3)	10.7 ± 23.0 (0.2–130)
Alkaline phosphatase (u/L)	264.0 ± 231.1 (18–1,092)
Aspartate transaminase (u/L)	603.9 ± 1,518.1 (13–8,270)
Alanine transaminase (u/L)	231.6 ± 394.8 (5–1,773)
Total bilirubin (mg/dL)	7.1 ± 10.3 (0.4–53)
Diagnostic laboratory values, mean ± SD (range)	
Soluble interleukin-2 receptor (U/mL)	19,955.7 ± 22,916.3 (1,536–95,716)
Ferritin (ng/mL)	29,532.9 ± 34,131.1 (1,765–138,705)
Triglycerides (mg/dL)	377.9 ± 638.9 (73–3,722)
Fibrinogen (mg/dL)	180.8 ± 131.3 (50–684)
Hemophagocytic syndrome diagnostic score, mean ± SD (range)	234.5 ± 28.3 (165–274)
Treatment, % (*n*)	
IV steroid	90 (28)
Chemotherapy (including etoposide)	51 (16)
Intravenous immunoglobulin	35 (11)
Rituximab	6 (2)
Anakinra	3 (1)

TABLE 2.
Etiology of Hemophagocytic Lymphohistiocytosis

Etiology	Prevalence, *n* (%)	28-d Mortality, %	1-yr Mortality
Infectious etiology	13 (45)	69	69
Viral	9 (29)	78	78
Bacterial	3 (10)	67	67
Fungal	1 (3)	0	0
Malignancy	11 (35)	64	91
Hematologic	10 (32)	60	90
Solid (germ cell) tumor	1 (3)	100	100
Autoimmune disease	2 (6)	50	50
Idiopathic	5 (16)	60	80

TABLE 3.
Characteristics of Patients Based on Survival at 28 d

Characteristics	Survivors at 28 d (*n* = 11)	Deceased at 28 d (*n* = 20)	*p*
Age	38.1	53.6	0.035
WBC (1,000/mm^3)	4.6	14.1	0.286
Hemoglobin (gm/dL)	9.8	10.7	0.333
Platelets (1,000/mm^3)	133.2	97.4	0.451
Aspartate transaminase (u/L)	404.5	713.6	0.563
Alanine transaminase (u/L)	246.9	223.2	0.934
Total bilirubin (mg/dL)	3.4	9.2	0.132
Acute Physiology and Chronic Health Evaluation II score	16.5	23.0	0.004
Soluble interleukin-2 receptor (U/mL)	13,680.1	25,626.4	0.230
Ferritin (ng/mL)	32,271.0	29,198.4	0.821
Fibrinogen (mg/dL)	220.5	157.8	0.221
Hemophagocytic syndrome diagnostic score	249.1	226.0	0.032
Time from symptoms to diagnosis (wk)	5.3	6.5	0.687
Need for mechanical ventilation	27.3%	90%	0.001
Need for continuous renal replacement therapy	18.2%	65%	0.023
Need for vasopressor	45.5%	95%	0.004
Acute liver failure	9.1%	40%	0.106
Steroid treatment	100%	85%	0.1745
Chemotherapy treatment	81%	35%	0.023

TABLE 4.
Individual Characteristics of Patients With Liver Failure

Case	Age	Model for End-Stage Liver Disease Score[a]	Alanine Transaminase[a]	Aspartate Transaminase[a]	Total Bilirubin[a]	Etiology of Hemophagocytic Lymphohistiocytosis	Renal Replacement Therapy	Liver Biopsy
1	21	25	47	45	15.8	Germ cell tumor	Yes	Massive hepatic necrosis
2	66	36	2,096	638	9.4	Idiopathic	Yes	No
3	75	33	96	268	53.0	Idiopathic	Yes	No
4	33	24	8,270	1,773	2.8	Herpes simplex virus viremia	Yes	No
5	35	25	97	98	7.1	Idiopathic	Yes	Massive hepatic necrosis
6	23	35	1,285	1,290	7.6	Acute lymphocytic leukemia	No	No
7	65	19	23	23	5.0	Myelodysplastic syndrome	No	Increased histiocytic infiltrate and increased Kupffer cells
8	60	35	615	147	4.2	Epstein-Barr virus	Yes	No
9	27	23	389	161	9.0	Diffuse large B-cell lymphoma	Yes	Diffuse involvement by abnormal lymphoid proliferation (related to lymphoma)

[a]Laboratory tests upon hospital admission.
All patients were on mechanical ventilation and a vasopressor.

(MHN) (2), histiocytic infiltrates (1), and lymphocytic infiltrates (1). Patients who developed ALF had elevated transaminases (AST and ALT) and MELD score upon admission to the hospital and were more likely to require mechanical ventilation compared with those who did not develop ALF.

DISCUSSION

HLH is a hyperinflammatory autoimmune syndrome that leads to multiple organ failure in the ICU. The systemic inflammation associated with HLH explains why fever and constitutional symptoms are the most common presenting symptoms in our study at 71%, similar to but lower than the up to 90% reported in other studies (3, 7, 10, 15). Most presenting symptoms are nonspecific and they can easily be confused with infections, autoimmune disease, or any kind of inflammatory state, which may explain the prolonged time between symptom onset and the confirmed diagnosis. The diagnosis of HLH has largely been based on HLH-2004 criteria, which includes sIL-2 and NK function as diagnostic criteria. These tests are often performed off-site, as was the case for our patients, taking days to weeks to return, limiting their utility in early HLH diagnosis (1). For these reasons, the HScore is often a more practical tool to estimate an individual's risk of HLH (3, 7). All patients but one had an HScore

TABLE 5.
Characteristics of Patients With and Without Acute Liver Failure

Characteristics	ALF, *n* = 9, Mean (SD)	No ALF, *n* = 22, Mean (SD)	*p*
Age (yr)	45.0 (20)	49.0 (19)	0.589
Alkaline phosphatase (u/L)[a]	331.9 (201)	237.4 (241.7)	0.358
Aspartate transaminase (u/L)[a]	1,435.3 (2,504.4)	264.0 (432)	0.049
Alanine transaminase (u/L)[a]	493.7 (591.9)	124.6 (176)	0.016
Total bilirubin (mg/dL)[a]	12.7 (15.6)	4.9 (6.3)	0.054
Model for end-stage liver disease score[a]	28.3 (6.3)	18.4 (7.9)	0.002
Acute Physiology and Chronic Health Evaluation II	21 (6.0)	20 (6.5)	0.846
Soluble interleukin-2 receptor (U/mL)	27,632.0 (30,635.1)	16,970.4 (18,765.6)	0.316
Ferritin (ng/mL)	34,655.4 (39,448.9)	27,437.3 (32,200.4)	0.607
Fibrinogen (mg/dL)	139.0 (52.6)	198.7 (153.7)	0.269
Hemophagocytic syndrome diagnostic score	223.4 (30.2)	238.5 (27.1)	0.209
Need for mechanical ventilation % (*n*)	100.0% (9)	54.5% (12)	0.030
Need for continuous renal replacement therapy % (*n*)	78% (7)	36.4% (8)	0.054
Need for vasopressor % (*n*)	100% (9)	68.2% (15)	0.077
28-d mortality % (*n*)	89% (8)	54.5% (12)	0.106
1-yr mortality % (*n*)	100% (9)	68.2% (15)	0.077
Biopsy results (4/9)	*n*		
Massive necrosis	2		
Increased histiocytic infiltrate and increased Kupffer cells	1		
Diffuse involvement by abnormal lymphoid proliferation (related to lymphoma)	1		

ALF = acute liver failure.
[a]At the time of hospital admission.

greater than 169, the proposed cutoff value for diagnosing HLH, giving a sensitivity of 97% (7). On the other side, Saeed et al (16) proposed a ferritin cutoff of 3,951 ng/mL in critically ill patients to improve the diagnostic utility of HLH. That cutoff would have missed five patients (16%) in our cohort, suggesting that this cutoff may not be sensitive enough alone to diagnose HLH in adult critically ill patients. Additionally, elevated ferritin concentrations are not specific to HLH, being associated with renal failure, liver injury, infections, and hematologic malignancies, and studies have described a low specificity of elevated ferritin concentrations alone as a screening tool for HLH (17).

In our study, critically ill HLH patients had a high mortality of 65% at 28 days after HLH diagnosis. Higher APACHE II score, older age, and organ failure were associated with a higher mortality rate, consistent with that observed in a general ICU population (18, 19). Although APACHE II score is proven to predict hospital mortality rate in sepsis, it is notable that these patients had a higher mortality rate than what expected from their APACHE II score (20). A smaller study from India

($n = 10$) also had a similar presentation, where the mean APACHE II score was 17.4, but their ICU and inhospital mortality were, respectively, 70% and 80% (21). This simply could be due to deviation from the mean in a relatively smaller sample, but it may also reflect the fact that the hyperinflammatory process in HLH causes more future organ damage than expected in other patients with sepsis and similar APACHE II score.

ALF was common in our HLH cohort, diagnosed in nine of 31 patients (29%). This is higher than what has been reported, with other studies describing only 1% and 7% as developing ALF during ICU admission (9, 10). This finding could be due to the differences in the patient cohort; Indiana University hospital is a referral center for liver transplant. All ALF patients had elevated liver enzymes and bilirubin upon hospital admission; however, the indication for admission included liver failure in only two HLH patients in our analysis. The remaining seven cases of ALF developed after hospital admission and may represent clinical deterioration to multiple organ dysfunction, as most of these required mechanical ventilation, vasopressor support, and renal replacement therapy at some point during their hospital stay. Because these patients who developed ALF had a significantly higher AST, ALT, and MELD score upon admission to the hospital, it suggests that liver involvement may not simply be due to disease progression and likely started earlier in the disease process, prior to hospital admission. This suggests that clinician should consider a high MELD score and transaminases at admission to prevent delayed diagnosis of HLH in the settings of liver dysfunction, as has been suggested by others (22).

The etiology of ALF in adults with HLH has not been clearly defined. In our study, four of nine patients with ALF had a liver biopsy. The pathognomonic finding of hemophagocytosis, histiocytic infiltrates, and increased Kupffer cells was found in only one of four liver biopsies. This finding itself is not enough to diagnose HLH, and one other study suggested that only half of their 12 patients with hepatic sinusoidal hemophagocytosis met the 2004 HLH criteria (23). The finding of lymphoma cell infiltration in one patient's liver biopsy explains the liver failure and etiology of HLH in that case. In two patients, biopsy showed MHN, characterized by diffuse multilobular and panacinar hepatic necrosis (24). The exact mechanism of MHN is not well known, but it has been associated with viral hepatitis, autoimmune disease, and drug-induced liver injury (25). These findings suggest that HLH should be considered in liver failure or hepatitis cases without a clear etiology, particularly if they have other supportive laboratory or clinical finding.

Treatment of HLH in ICU patients is challenging due to a high severity of illness and similar presentation to other critical illnesses. Primary treatment is supportive care and treatment of the causative disease if one is identified. Further therapies focus on decreasing the hyperinflammatory state. In our cohort, most patients were treated with standard of care corticosteroids, but only half of the patients were able to receive full HLH 2004-recommended treatment, which includes administration of chemotherapeutic agents such as etoposide. As reported in previous studies, we found that patients who received chemotherapy with etoposide had a higher survival rate (18). However, sicker patients were less likely to receive chemotherapy, as evidenced by an average APACHE II score of 17.1 than 23.8 for those who received and did not receive etoposide. Therefore, it is difficult to conclude whether etoposide administration itself improved survival or if the observed survival benefit was due to milder disease in the treatment group. Anakinra, a human interleukin (IL)-1 receptor antagonist protein, was used in one of our patients. Anakinra in combination with intravenous immunoglobulin for treatment of HLH has been described in a small retrospective study, which found a 50% survival rate for ICU patients treated with this combination (26). Other proposed treatments for HLH include the anti-IL-6 antibody tocilizumab, which has been used for a number of diseases causing cytokine storm, most recently coronavirus disease 2019, in which severe disease shares some characteristics with HLH (27, 28). Stem-cell transplant has also been suggested as a salvage therapy and was used in one of our patients with HLH due to underlying lymphoma (27). Current recommendations suggest multidisciplinary input to tailor therapy to each patient depending on their comorbidities, HLH trigger, presentation, and severity of illness.

There are limitations to this study. First, it is a retrospective analysis performed at a single tertiary-care center, a referral center for liver transplant. Due to the retrospective nature, data were collected from chart reviews and relied on documentation of symptoms and clinical findings, which due to their nonspecific nature may not have been recorded. The relatively small sample size and retrospective nature precluded

multivariate analysis. Furthermore, treatment and diagnostic algorithms reflect our single-center experience. Future prospective, multicenter studies are needed to confirm our findings, particularly the correlation of high MELD score and elevated transaminases with early diagnosis of HLH-associated ALF and as markers of a poor prognosis in HLH.

CONCLUSIONS

HLH is a rare, life-threatening, and likely underrecognized disease that carries very high mortality when diagnosed in critically ill patients. It should be suspected in patients with constitutional symptoms and should be considered in patients who develop ALF, especially in the setting of elevated ferritin and high HScore. ALF may present early or late in the course of the disease especially in patients with high admission MELD score and carries a very high mortality. Treatments include targeted therapies to the triggering disease, and the use of corticosteroids and chemotherapeutic agents, but ICU patients diagnosed with HLH and ALF were often too sick to receive the all recommended therapies. Given the high mortality, future studies should further explore the role for early screening for HLH and associated ALF and on the role of early, aggressive therapy in this population, particularly with new therapies that may mitigate the adverse effects of traditional chemotherapies and therefore better tolerated by critically ill HLH patients.

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