

Prognostic Factors of Death in 151 Adults With Hemophagocytic Syndrome: Etiopathogenically Driven Analysis

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Abstract

Objective: To characterize the etiologies and clinical features at diagnosis of patients with hemophagocytic lymphohistiocytosis (HLH) and correlate these baseline features with survival using an etiopathogenically guided multivariable model.

Patients and Methods: The Spanish Group of Autoimmune Diseases HLH Study Group, formed in 2013, is aimed at collecting adult patients with HLH diagnosed in internal medicine departments between January 3, 2013, and October 28, 2017.

Results: The cohort consisted of 151 patients (91 men; mean age, 51.4 years). After a mean follow-up of 17 months (range, 1-142 months), 80 patients died. Time-to-event analyses for death identified a worse survival curve for patients with neoplasia ($P < .001$), mixed microbiological infections ($P = .02$), and more than 1 infection ($P = .01$) and glucocorticoid monotherapy ($P = .02$). According to univariate analyses, platelets of less than $100,000/\text{mm}^3$ (hazard ratio [HR], 3.39; 95% CI, 1.37-8.40), leukopenia (HR, 1.81; 95% CI, 1.01-3.23), severe hyponatremia (HR, 1.61; 95% CI, 1.02-2.54), disseminated intravascular coagulation (HR, 1.87; 95% CI, 1.05-3.34), bacterial infection (HR, 1.99; 95% CI, 1.09-3.63), mixed microbiological infections (HR, 3.42; 95% CI, 1.38-8.46), and 2 or more infectious triggers (HR, 2.95; 95% CI, 1.43-6.08) were significantly associated with death. In contrast, peripheral adenopathies (HR, 0.63; 95% CI, 0.40-0.98) and the immunosuppressive drug/intravenous immunoglobulin/biological therapies (HR, 0.44; 95% CI, 0.20-0.96) were protective against all-cause mortality. Multivariable Cox proportional hazards regression analysis identified 2 or more infectious triggers (HR, 3.14; 95% CI, 1.28-7.68) as the only variable independently associated with death.

Conclusion: The mortality rate of adult patients diagnosed with HLH exceeds 50%. Infection with more than 1 microbiological agent was the only independent variable associated with mortality irrespective of the underlying disease, epidemiological profile, clinical presentation, and therapeutic management.

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Hemophagocytic lymphohistiocytosis (HLH, also called hemophagocytic syndrome) is an immune-mediated life-threatening disease caused by impaired natural killer (NK) and cytotoxic T-cell function.¹ It was first described in 1939 by pediatricians, and therefore the disease has been characterized overwhelmingly in children, although the number of studies in adults is increasing. Etiopathogenically, genetic defects are linked to the development of HLH in children, whereas adults have a more complex scenario, with 2 main groups of etiological factors: underlying diseases and conditions that increase the risk of developing HLH, and external factors that initiate the pathogenic hyperinflammatory process (overwhelmingly infections).² The heterogeneous pathogenic scenario in adults, in which different predisposing diseases and conditions are often mixed with different triggers, together with the high mortality rate, makes HLH one of the most complex and life-threatening clinical diseases.

Prognostic studies in large cohorts of adult patients with HLH are limited. Some studies have focused on patients with a specific underlying disease or trigger, including HLH-related lymphoma,³ Still disease,⁴ lupus,⁵ human immunodeficiency virus infection,⁶ and Epstein-Barr virus infection.⁷ However, large studies include etiologically unselected patients, the largest of which are recently reported French studies including 162 patients,^{8,9} and a Chinese study including 205 patients.¹⁰ In these studies, mortality rates varied widely, and a large list of prognostic factors was identified. Several clinical factors contribute to this heterogeneity, including significant differences in the frequency of underlying diseases, the rate of patients recruited from intensive care units (ICUs), the definition of the main outcome studied (death), and the statistical approaches used. These factors make the identification of independent prognostic factors of survival that could be extrapolated and therefore generalized to other HLH adult populations difficult.

The aim of this study was to characterize the etiologies and clinical features at diagnosis in a large cohort of Spanish adult patients with HLH and correlate these baseline features with survival using an etiopathogenically guided multivariable statistical model.

METHODS

Patients

The HLH Study Group of the Spanish Group of Autoimmune Diseases (Grupo de Enfermedades Autoinmunes Sistémicas) was formed in 2013 with the aim of collecting a large series of Spanish adult patients with HLH diagnosed in internal medicine departments with substantial experience in the management of patients with systemic diseases. Between January 3, 2013, and October 28, 2017, 151 consecutive patients who fulfilled at least 5 of the 8 criteria proposed by the Histiocytosis Society in 2004¹¹ were included. The study protocol was approved by the Clinical Research Ethics Committee of the Hospital Clínic of Barcelona (HCB/2016/0183) and complied with the ethical standards of the Declaration of Helsinki. The institutional review board waived the need for informed consent because of the retrospective design and the high rate of mortality.

Definition of Variables

The date of HLH diagnosis was defined as confirmation of fulfillment of HLH criteria by the attending physician. For patients with recurrent hemophagocytic syndrome, only the first episode was considered. The end of follow-up was defined according to the last recorded Spanish National Healthcare System visit, which was the principal source of information on the health status. The primary outcome was all-cause mortality.

Variables assessed as prognostic factors for survival were collected by retrospective review of individual medical charts and classified into 4 groups:

1. Epidemiological features. Age at diagnosis, sex, country of birth, active immunosuppression (defined as the use of glucocorticoids [GCs], immunosuppressive drugs [IDs], and/or biological therapies ≥ 1 month before HLH diagnosis), and underlying diseases/conditions present at HLH diagnosis, classified as neoplasia, autoimmune/rheumatic diseases, and others (chronic viral infections, solid organ transplantation).
2. HLH features. Clinical features and organ involvements directly related to HLH were defined according to standard definitions.¹ Laboratory values were collected as the

maximum or minimum abnormal value measured during the HLH diagnostic process. Hemophagocytosis was defined as histological evidence of activated macrophages engulfing erythrocytes, platelets, and/or nucleated cells or their precursors, in bone marrow smears and/or biopsy of bone marrow, liver, spleen, or lymph node.⁸ The HScore¹² was calculated only in those patients in whom all the values for the items included in the score were available.

3. Infectious trigger. Clinical/microbiological evidence of active bacterial, viral, parasitic, and/or fungal infection identified during the HLH diagnostic process, confirmed by standard diagnostic procedures used in the standard of care practice of internal medicine. As a key differentiating aspect from previous studies, we classified infectious diseases as underlying chronic infections (mainly chronic human immunodeficiency virus and hepatitis C virus infections) and acute infections (diagnosed during the HLH diagnostic process as playing an acute role in triggering the hyperinflammatory response).
4. Therapeutic interventions. The HLH-related therapeutic regimens were classified as GC monotherapy, GC combined with other drugs (IDs, intravenous immunoglobulins [IVIGs], and/or biologics), and chemotherapy (including etoposide-based and other regimens).

Statistical Analyses

Descriptive data are presented as mean and SD or median and interquartile range for continuous outcomes and number and percentage (%) for categorical outcomes. Time-to-event analyses for death are presented as Kaplan-Meier curves. An etiopathogenically guided statistical approach was designed on the basis of the most-commonly accepted hypothesis of the etiopathogenesis of HLH in adults¹: epidemiological features, underlying diseases, and active immunosuppression at HLH diagnosis were considered as HLH-independent variables, whereas HLH clinical features, infectious triggers, and therapeutic interventions were considered as HLH-dependent variables forming part of the disease presentation and management. Univariate Cox proportional hazards regression analyses

TABLE 1. Main Clinical, Histopathological, and Laboratory Features^{a,b}

Feature	N	Patients	%
Epidemiology			
Age at diagnosis (y), mean ± SD	150	51.4±21.5	
Sex: male	151	91	60.3
Born outside Spain	151	26	17.2
Underlying diseases^c			
Autoimmune/rheumatologic diseases	151	53	35.1
Systemic lupus erythematosus	151	13	8.6
Inflammatory bowel disease	151	7	4.6
Still disease	151	7	4.6
Rheumatoid arthritis	151	6	4.0
Inflammatory myopathies	151	4	2.6
Mixed connective tissue disease	151	4	2.6
Vasculitis	151	3	2.0
Other autoimmune diseases	151	9	6.0
Neoplasia	151	48	31.8
T/NK-cell lymphoma	151	14	9.3
B-cell lymphoma	151	12	7.9
Other hematological neoplasia	151	11	7.3
Solid neoplasia	151	11	7.3
Chronic viral infections	151	32	21.2
Transplantation	151	8	5.3
No underlying disease identified	151	42	27.8
Active immunosuppressive treatment	151	42	27.8
Clinical presentation			
a. Symptoms/organs involved			
Duration of symptoms (wk), mean ± SD	151	3.7±4.5	
Fever (>37.5°C)	151	140	92.7
Splenomegaly	151	96	63.6
General symptoms	151	71	47.0
Hepatomegaly	151	76	50.3
Peripheral adenopathies	151	74	49.0
Pulmonary involvement	151	70	46.4
Renal involvement	151	51	33.8
Gastrointestinal involvement	151	46	30.5
Skin lesions	151	42	27.8
CNS involvement	151	35	23.2
Arthralgias/myalgias	151	29	19.2
b. Hematological & coagulation			
Anemia			
Hemoglobin <12 g/dL	149	140	94.0
Hemoglobin <9 g/dL	149	104	69.8
Hemoglobin <7 g/dL	149	34	22.8
Thrombocytopenia			
Platelets <150,000 cells per mm ³	150	136	90.7
Platelets <100,000 cells per mm ³	150	128	85.3
Platelets <10,000 cells per mm ³	150	21	14.0
Leukopenia (leukocytes <4000 cells per mm ³)	150	115	76.7
Neutropenia			
Neutrophils <1500 cells per mm ³	148	89	60.1
Neutrophils <1000 cells per mm ³	148	69	46.6
Neutrophils <500 cells per mm ³	148	34	23.0

Continued on next page

TABLE 1. Continued

Feature	N	Patients	%
Clinical presentation, continued			
Hypofibrinogenemia (fibrinogen <1.5 g/L)	146	30	20.5
Disseminated intravascular coagulation	151	20	13.2
c. Biochemical			
Hyperferritinemia			
Ferritin >500 ng/mL	140	135	96.4
Ferritin >1000 ng/mL	140	127	90.7
Ferritin >10,000 ng/mL	140	48	34.3
Hypertriglyceridemia			
Triglycerides >150 mg/dL	140	128	91.4
Triglycerides >265 mg/dL	140	93	66.4
Hyponatremia			
<135 mmol/L	148	92	62.2
<130 mmol/L	148	42	28.4
Raised ALT transaminase			
ALT transaminase >40 IU/L	148	114	77.0
ALT transaminase >100 IU/L	148	78	52.7
Raised AST transaminase			
AST transaminase >40 IU/L	147	117	79.6
AST transaminase >100 IU/L	147	84	57.1
Raised lactate dehydrogenase			
Lactate dehydrogenase >500 IU/L	146	115	78.8
Lactate dehydrogenase >1000 IU/L	146	74	50.7
d. Hemophagocytosis			
Histopathological confirmation	148	138	93.2
e. HScore, ^d median (IQR)			
	126	230 (200-267)	

^aALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; IQR = interquartile range; NK = natural killer.

^bUnless otherwise specified, the values are number (%).

^cPatients may have more than 1 underlying disease.

^dOnly calculated in patients with all items measured/carried out (n=126).

were performed to study the crude measure of association between all variables and death. Statistically significant HLH-dependent variables were entered into a multivariable Cox proportional hazards regression analysis adjusted for HLH-independent variables, which permitted identification of variables independently associated with all-cause mortality. The hazard ratios (HRs) and their 95% CIs obtained in the Cox regression analysis were calculated. All significance tests were 2-tailed, and values of $P < .05$ were considered significant. All analyses were conducted using the R version 3.0.3 for Windows statistical software package.

RESULTS

Baseline Characterization

Baseline characteristics are summarized in Table 1. The cohort consisted of 151 patients,

including 91 (60%) males (male:female ratio, 1.5:1), with a mean age at diagnosis of 51.4 ± 21.5 years (range, 14-92 years); 26 (17%) patients were born outside Spain. The main group of underlying diseases consisted of autoimmune/rheumatic diseases in 53 (35%) patients, neoplasia in 48 (32%), chronic viral infections in 32 (21%), and solid organ transplantation in 8 (5%); 29 (19%) patients had 1 or more underlying disease, whereas 42 (28%) had no identified underlying disease/condition. Active immunosuppressive treatment was reported in 42 (28%) patients at HLH diagnosis. The main clinical HLH features included fever in 140 (93%) patients, splenomegaly in 96 (64%), hepatomegaly in 76 (50%), peripheral adenopathies in 74 (49%), general symptomatology in 71 (47%), and pulmonary involvement in 70 (46%) patients. Other clinical manifestations are presented in Table 1. The most common hematological abnormalities were anemia in 140 of 149 (94%) patients, thrombocytopenia in 136 of 150 (91%), and leukopenia in 115 of 150 (77%). The most frequent laboratory abnormalities included raised ferritin levels in 135 of 140 (96%), raised triglycerides in 128 of 140 (91%), raised AST transaminase in 117 of 147 (80%), raised lactate dehydrogenase in 115 of 146 (79%), and hyponatremia in 92 of 148 (62%). Soluble IL-2 receptor (CD25) levels were raised in 20 of 25 (80%), and NK-cell activity was absent or lower in 15 of 18 (83%). Hemophagocytosis was confirmed in 138 of 148 (93%) cases (in 3 cases there was no histopathological study, due to sudden death, or autopsy results).

Infectious triggers (see Supplemental Table 1, available online at <http://mcpiqojournal.org/>) were diagnosed in 95 (63%) patients, including acute viral infections in 47 (49%) patients, bacterial infections in 33 (35%), parasitic infections in 9 (9.5%) (including 8 cases of Leishmaniasis, which is endemic in Spain), and fungal infections in 13 (14%); 14 patients presented infection by 2 different microorganisms; specific anti-infective agents were administered according to standard therapeutic recommendations followed in internal medicine departments.

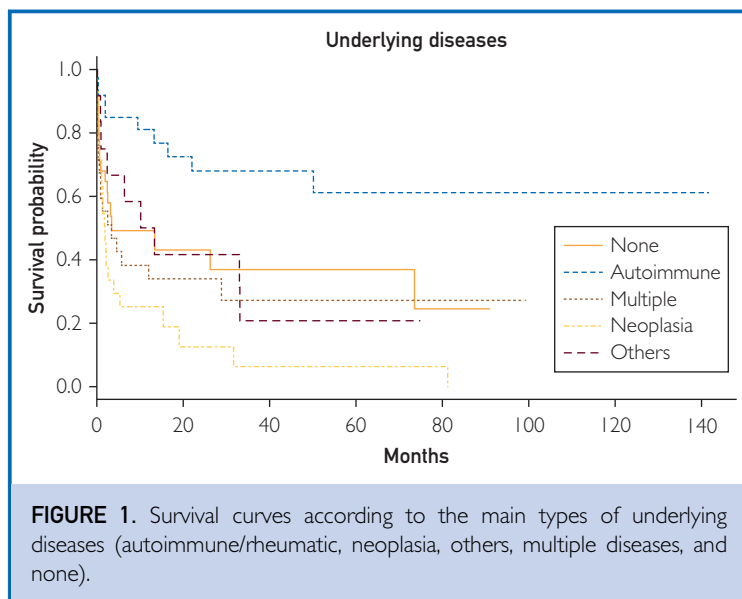
Specific therapies for HLH included glucocorticoids in 129 (85%) patients, etoposide in 28 (19%), cyclosporine A in 28 (19%), IVIGs in 22 (15%), and rituximab in 12 (8%);

19 (13%) patients did not receive IDs. The list of drugs and the therapeutic regimens used are summarized in [Supplemental Table 2](#) (available online at <http://mcpiqjournal.org/>). Admission in ICU was required in 59 (39%) patients.

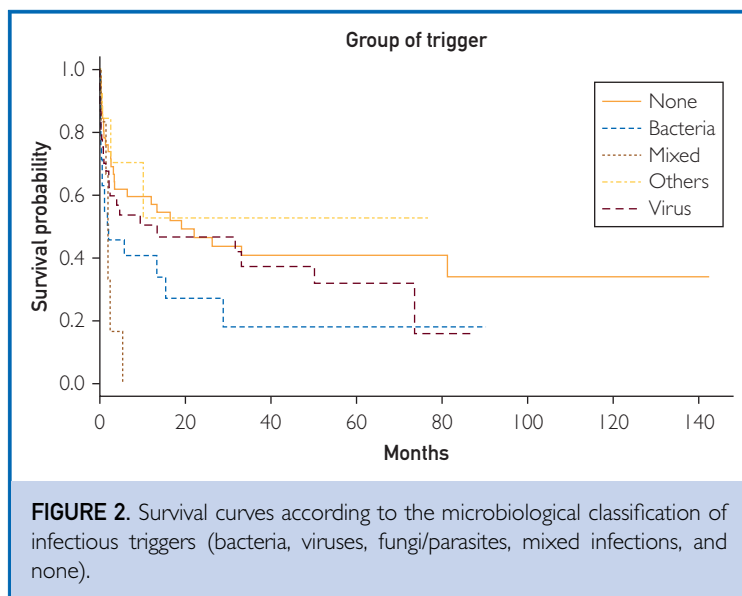
Survival Analysis

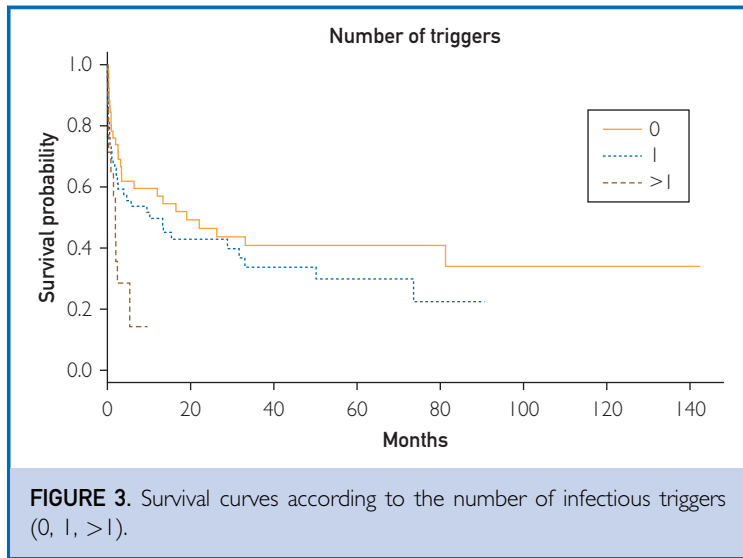
After a mean follow-up of 17 months (range, 1-142 months), 80 patients died. [Supplemental Figure 1](#) (available online at <http://mcpiqjournal.org/>) shows the survival curve of the entire cohort; survival at 1, 2, 3, 6, and 12 months was 73.6%, 66.3%, 59.4%, 52.8%, and 48.8%, respectively. Time-to-event analyses for death (Kaplan-Meier curves) were made according to the main types of underlying diseases (autoimmune/rheumatic, neoplasia, others, multiple diseases, and none), microbiological classification of infectious triggers (bacteria, viruses, fungi/parasites, mixed infections, and none), number of infectious triggers (0, 1, >1), and HLH-specific therapeutic regimens (GC monotherapy, GC + other drugs, etoposide-based chemotherapy, other chemotherapies, and none). [Figure 1](#) shows that the best survival curve was in patients with underlying autoimmune/rheumatic diseases and the worst was in those with neoplasia (log-rank $P < .001$). [Figure 2](#) shows that the worst survival curves were for patients with mixed microbiological infections and those with bacterial infections (log-rank $P = .02$), whereas [Figure 3](#) shows that the worst survival curve was in patients with more than 1 infectious trigger (log-rank $P = .01$). [Supplemental Figure 2](#) (available online at <http://mcpiqjournal.org/>) shows that the best survival curves were in patients treated with IDs/IVIGs/biologics and etoposide-based therapies and the worst was in those treated with GC monotherapy (log-rank $P = .02$).

[Table 2](#) summarizes the HRs obtained in the univariate Cox proportional hazards regression analyses. The HLH-independent variables associated with death were age (HR, 1.03; 95% CI, 1.02-1.04), male sex (HR, 1.61; 95% CI, 1.01-2.56), and underlying neoplasia (HR, 1.84; 95% CI, 1.01-3.37). With respect to the HLH-dependent variables, platelets less than $100,000/\text{mm}^3$ (HR, 3.39; 95% CI, 1.37-8.40), leukopenia (HR, 1.81; 95% CI, 1.01-3.23), severe hyponatremia (HR, 1.61; 95% CI, 1.02-2.54), disseminated intravascular coagulation (HR, 1.87; 95% CI,



1.05-3.34), bacterial infection (HR, 1.99; 95% CI, 1.09-3.63), mixed microbiological infections (HR, 3.42; 95% CI, 1.38-8.46), and 2 or more infectious triggers (HR, 2.95; 95% CI, 1.43-6.08) were associated with death. In contrast, underlying autoimmune/rheumatic diseases (HR, 0.34; 95% CI, 0.16-0.74), peripheral adenopathies (HR, 0.63; 95% CI, 0.40-0.98), and ID/IVIG/biological therapies (HR, 0.44; 95% CI, 0.20-0.96) were protective against all-cause mortality.





These variables were entered into a multivariable Cox proportional hazards regression analysis that identified 2 or more infectious triggers (HR, 3.14; 95% CI, 1.28-7.68) as the only variable independently associated with death (Table 3).

DISCUSSION

One of the most critical clinical conditions in adults is HLH, with an all-cause mortality rate reported in large series ranging between 42%⁹ and 75%.¹³ Eight studies have analyzed prognostic factors in large cohorts of adults (>50 patients) in the last 10 years (see Supplemental Table 3, available online at <http://mcpqjournal.org/>) and found that most factors identified preexist the HLH diagnosis (epidemiological features, underlying diseases). Epidemiological features were key prognostic markers, especially age,¹³⁻¹⁶ but also male sex,^{13,15} together with underlying diseases, with patients with underlying neoplasia^{9,10,14,15,17,18} having a poor prognosis compared with other etiologies. With respect to HLH presentation, only splenomegaly¹³ was identified as a prognostic factor among HLH-related clinical features, while the number of prognostic laboratory markers was higher, including thrombocytopenia,^{10,13,14,17} creatinine,¹⁵ prothrombin time,^{10,16} ferritin,¹⁵ and fibrinogen.¹⁶ Other prognostic factors identified were closely related to ICU admission (sequential organ failure assessment [SOFA]

score, shock, and requirement for life-sustaining therapies such as renal replacement).^{14,16,17} In total, these studies identified 13 different prognostic factors.

The wide list of prognostic factors identified until now for adult HLH may be due to several factors. First, the different frequencies of underlying diseases (which have *per se* a considerable influence on survival) included in each study; although all but 1 study¹⁵ identify neoplasia as the most frequent underlying disease, the frequency ranges widely from 30%¹⁴ to 77%¹⁷; in addition, it is unclear how the frequent overlap between different etiologies (especially between underlying diseases and infections) was defined and analyzed. Another source of heterogeneity is that some studies included only patients admitted to the ICU^{14,16,17} and different definitions of the primary outcome, including hospital mortality,^{16,17} all-cause mortality,^{10,13,15,18} and 1-month mortality.^{9,14} The statistical approach was also heterogeneous, mainly including multivariable analysis using logistic regression models with different selection methods for variables at model entry, even though logistic regression is not recommended for the analysis of time-dependent outcomes.¹⁹ Few studies used more appropriate time-to-event analysis approaches, such as Kaplan-Meier^{9,18} or Cox-regression¹⁰ models that allowed quantification of the measure of effect by means of HRs depending on the time of follow-up, whereas no study considered adjustment to control the confounding effects of overlapping or preexisting HLH variables.

Our results confirm, in the crude univariate analysis, the prognostic factors most frequently reported in previous studies, including age, male sex, underlying disease, thrombocytopenia, disseminated intravascular coagulation, infections, and therapeutic interventions. However, we also identified other, unreported factors, such as adenopathies, leukopenia, and severe hyponatremia. In the statistical adjustment, we used age and sex (usually used as variables of adjustment) but added underlying diseases. This pretest statistical design was based not only on the expected influence on patient survival of patient having a specific underlying disease, but also because some clinical and laboratory parameters identified in the crude analysis are closely linked to the clinical expression

of the main underlying diseases (autoimmune diseases and neoplasia). According to the multivariable Cox proportional hazards regression analysis adjusted for HLH-independent variables, infection with more than 1 agent remained the only independent variable associated with survival in adult patients with HLH, an association that should be considered significant irrespective of the underlying disease, epidemiological profile, clinical presentation, and therapeutic management.

Therefore, we identified infection as the key independent factor for survival in adults with HLH. A few studies have focused on the role of acute infectious triggers in HLH survival, mainly in pediatric patients,^{20,21} but also in adults treated with biological agents.²² However, some descriptive studies have reported higher mortality rates in patients presenting with bacterial infections^{13,23,24} or co-infections.^{21,25} Our study reports, for the first time, that both the variety and number of infectious triggers implicated in HLH have a considerable influence on survival using time-to-event statistical models; the best survival curve was found for patients with parasitic/fungal infections, followed by those with viral infections, whereas the worst survival curves were for those with bacterial infections and multiple microbiological infections (of whom 71% also had bacterial infections in association with other microorganisms). Leishmaniasis, an endemic infection in Spain, was the most frequent parasitic infection related to HLH (8 cases, all born in Spain, of which 7 were reported from Madrid). These findings should encourage efforts to detect (and therefore treat) the infectious triggers of HLH (especially bacterial infections) as early as possible.

The time-to event analyses confirmed a worse prognosis of HLH in adult patients with underlying neoplasia,¹⁸ and the protective effect of having an autoimmune/rheumatic disease; descriptive studies have also suggested a better prognosis for HLH related to autoimmune diseases,¹³ with mortality rates of 13% in HLH-related autoimmune diseases,²⁶ 9.5% in HLH-related adult-onset Still disease,⁴ and 3% in HLH-related lupus.⁵ This compares with mortality rates of more than 80% in HLH-related lymphoma,¹³ and the figure

TABLE 2. Univariate Analyses of Risk Factors for All-Cause Mortality^{a,b}

Variable	All-cause mortality (n=80)	
	Univariate HR (95% CIs)	P
Epidemiological variables		
Age at diagnosis (y)	1.03 (1.02-1.04)	<.001
Sex: male	1.61 (1.01-2.56)	.04
Underlying disease grouped		
None	Reference	
Neoplasia	1.84 (1.01-3.37)	.05
Autoimmune/rheumatic disease	0.34 (0.16-0.74)	.006
Others	0.98 (0.45-2.17)	.97
Multiple (more than 1)	1.24 (0.66-2.35)	.51
Active ID therapies	0.76 (0.45-1.28)	.30
Clinical variables		
Fever (>37.5°C)	0.93 (0.43-2.03)	.86
Splenomegaly	0.88 (0.56-1.39)	.59
Hepatomegaly	1.24 (0.80-1.92)	.34
Peripheral adenopathies	0.63 (0.40-0.98)	.04
Pulmonary involvement	1.40 (0.91-2.18)	.13
CNS involvement	1.11 (0.64-1.91)	.71
Skin lesions	0.82 (0.50-1.37)	.45
Gastrointestinal involvement	1.03 (0.65-1.65)	.89
Renal involvement	1.33 (0.84-2.10)	.23
Hemoglobin <9 g/dL	1.71 (0.96-3.05)	.07
Platelets <100,000 cells per mm ³	3.39 (1.37-8.40)	.008
WBC <4000 cells per mm ³	1.81 (1.01-3.23)	.05
Neutrophils <1000 cells per mm ³	1.48 (0.90-2.42)	.12
Triglycerides >150 mg/dL	1.24 (0.54-2.86)	.61
Natremia <130 mmol/L	1.61 (1.02-2.54)	.04
AST transaminase >100 IU/L	0.89 (0.57-1.40)	.62
ALT transaminase >100 IU/L	0.81 (0.52-1.25)	.34
Lactate dehydrogenase >450 IU/L	0.84 (0.54-1.31)	.45
Ferritin >500 ng/mL	3.05 (0.42-21.97)	.27
Fibrinogen <1.5 g/L	1.29 (0.76-2.22)	.35
Disseminated intravascular coagulation	1.87 (1.05-3.34)	.03
Histopathological hemophagocytosis	1.71 (0.63-4.68)	.30
HScore (≥169)	1.29 (0.59-2.84)	.53
Infectious trigger		
Presence of infectious trigger	1.53 (0.96-2.45)	.07
Microbiological classification		
No infection	Reference	
Bacteria	1.99 (1.09-3.63)	.03
Virus	1.36 (0.79-2.34)	.28
Fungi/parasites	0.78 (0.27-2.24)	.65
Mixed	3.42 (1.38-8.46)	.008
Number of infectious triggers		
0	Reference	
1	1.38 (0.85-2.24)	.20
≥2	2.95 (1.43-6.08)	.003
Therapeutic interventions		
No immunosuppressive drugs	Reference	
Glucocorticoid monotherapy	1.21 (0.60-2.44)	.60

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TABLE 2. Continued

Variable	All-cause mortality (n=80)	
	Univariate HR (95% CIs)	P
Therapeutic interventions, continued		
ID/IVIG/biological therapies	0.44 (0.20-0.96)	.04
Chemotherapy	0.69 (0.34-1.39)	.30

^aALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; HR = hazard ratio; ID = immunosuppressive drug; IVIG = intravenous immunoglobulin; WBC = white blood cell.
^bValues are represented as HRs and 95% CIs.

may be even higher in patients with HLH-related NK/T-cell lymphoma.²⁷ We also analyzed the role of therapeutic interventions in survival, and found better trends in patients treated with GCs plus other agents (IDs, IVIGs, or biologics) and those treated with etoposide. In contrast, patients treated with

GC monotherapy and those who did not receive specific HLH therapy had the worst survival curves. Studies in children^{20,28,29} and adults^{5,8,30} have found similar results. These studies, together with our results, highlight the differentiated prognosis of HLH according to the underlying disease and the need for more-intensive immunosuppressive therapy than monotherapy with GCs. The survival rates reported in prognostic HLH studies including multiple etiologies should always be evaluated taking into account the frequency of each underlying disease in the corresponding cohort, and a lower survival rate should be expected in cohorts in which neoplasia predominates (clearly related to the high rate of high-grade associated hematological neoplasia) and a better rate in cohorts with a predominance of underlying autoimmune/rheumatic disease (as observed in our study).

Our results and those of other studies analyzing prognostic factors associated with survival in adult HLH should be evaluated with caution because of the retrospective design and the lack of an international consensus on the management and treatment of adult HLH. Because of the rarity of the disease and the often-life-threatening presentation, prospective studies or randomized controlled trials in patients with HLH are extremely difficult, and it may be anticipated that the level of evidence will remain limited to retrospective studies. An additional limitation of our study, as occurs in retrospective multicenter studies, is the lack of a central review of laboratory and histopathological data to ensure a homogeneous diagnostic approach. Therefore, we are now working on the development of a Spanish diagnostic and therapeutic protocol for adult patients with HLH, searching for a nationwide homogeneous approach to the disease. One additional future task could be the worldwide collection and analysis of larger real-life data sets involving the main specialties involved in the care of these patients (intensive care, internal medicine, rheumatology, pediatrics, and hematology) and specific etiologically driven substudies considering the variety and combinations of the underlying diseases and infectious triggers. The complexity of these patients, in whom different etiopathogenic scenarios coexist, together with a mortality

TABLE 3. Adjusted Multivariable Analysis of Risk Factors for Survival^{a,b}

Variable	All-cause mortality (n=80)	
	Multivariable HR (95% CIs) ^c	P
Peripheral adenopathies	0.76 (0.45-1.28)	.30
Platelets <100,000 cells per mm ³	1.92 (0.72-5.15)	.20
WBC <4000 cells per mm ³	1.54 (0.83-2.85)	.17
Natremia <130 mmol/L	1.41 (0.84-2.39)	.20
Disseminated intravascular coagulation	1.56 (0.81-3.00)	.19
Number of infectious triggers		
0		
1	0.95 (0.56-1.61)	.85
≥2	3.14 (1.28-7.68)	.01
Microbiological classification		
NC ^d		
No infection		
Bacteria		
Virus		
Fungi/parasites		
Mixed		
Therapeutic interventions		
No immunosuppressive drugs		
Reference		
Glucocorticoid monotherapy	1.37 (0.65-2.92)	.41
ID/IVIG/biological therapies	0.78 (0.33-1.85)	.57
Chemotherapy	0.71 (0.32-1.54)	.38

^aID = immunosuppressive drug; IVIG = intravenous immunoglobulin; NC = not calculated; HR = hazard ratio; WBC = white blood cell.

^bValues are represented as HRs and 95% CIs.

^cMultivariable Cox proportional hazards regression analysis adjusted for age at diagnosis, sex, and underlying disease group.

^dTo avoid multicollinearity with the number of triggers, the trigger group was not included in the model.

rate of nearly 50%, poses a considerable clinical and therapeutic challenge.

CONCLUSION

This is the first study that characterizes the etiologies and clinical features at diagnosis of patients with HLH and correlates these baseline features with survival using an etiopathogenically guided multivariable model. The results suggest that the mortality rate of adult patients diagnosed with HLH exceeds 50%. There was worse survival for patients with neoplasia and mixed microbiological infections, with 1 or more infections being the only independent variable associated with mortality, irrespective of the underlying disease, epidemiological profile, clinical presentation, and therapeutic management.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://mcpiqjournal.org/>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: GC = glucocorticoid; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; ID = immunosuppressive drug; IVIG = intravenous immunoglobulin; NK = natural killer

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