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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/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 2004[11] were included. The study protocol was approved by the Clinical Research Ethics Committee of the Hospital Clinic 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 $\geq$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