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A Risk Model Based on sCD25 for Early Mortality in Adult Patients with Hemophagocytic Lymphohistiocytosis

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Introduction: Hemophagocytic lymphohistiocytosis (HLH), a life-threatening hyperinflammatory syndrome, is characterised by rapid disease progression and high early mortality. We aim to investigate the characteristics of the early death (ED) in adults with HLH and develop a reliable risk model to predict early mortality.

Materials and Methods: Between September 2013 and July 2024, 254 adult patients with HLH were examined. Clinical data including presentation, triggers, treatments, and laboratory results were reviewed. Cases were randomly divided into training and validation cohorts using R. Independent risk factors for 60-day mortality were identified, leading to the development of a risk model using nomogram.

Results: 26.4% (67/254) of patients with HLH died within 60 days. Cox multivariate analyses identified independent risk factors for 60-day mortality, including PLT $<100\times10^9$/L ($P = 0.006$), sCD25 ≥12000 U/mL ($P = 0.046$) and EBV DNA copies ≥ 10000 copies/mL ($P = 0.006$). And the C-index, a measure of predictive performance, of the ED risk model by nomogram yielded values of 0.698 and 0.654 in the training cohort and validation cohort, respectively. The calibration curve demonstrated that the prediction outcome was correlated with the observed outcome. Assigning values to each risk factor, this resulted in the stratification of the 254 patients into low-risk groups (n = 54), intermediate-risk groups (n = 184), and high-risk groups (n = 16), with the corresponding 60-day overall survival rates being 90.7%, 71.7%, and 37.5%, respectively.

Conclusion: The novel ED risk model can effectively and precisely identify high-risk adult patients with HLH, offering appropriate clinical recommendations.

Keywords: hemophagocytic lymphohistiocytosis, early mortality, risk model, sCD25, nomogram

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare yet frequently life-threatening hyperinflammatory syndrome.[1] The common manifestations of HLH in patients include fever, hepatosplenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia and hemophagocytosis in bone marrow, spleen, or lymph nodes.[2] Depending on the etiology, HLH is divided into primary HLH (pHLH) and secondary HLH (sHLH). pHLH can be diagnosed at any age and is caused by genetic damage to lymphocyte cytotoxicity or defects in genes related to inflammatory activity. sHLH is common in adults and can be caused by infection or associated with systemic rheumatism or malignancy. The rapid early progression of this disease is due to a complex interplay of genetic defects, susceptibility factors and various triggers, with the result that the median overall survival (OS) of adult patients with HLH is only 3.2 months, and the 1-year overall survival rate is 35%.[3] For patients without treatment, the median survival time is limited to a mere 1.8–2.2 months.[4] Among patients with HLH who do not undergo hematopoietic stem cell transplantation (HSCT), the majority do not survive beyond two months.[5] Identifying effective methods to alert patients of the likelihood of early death is a crucial step in improving their prognosis.

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Some studies have been conducted to provide models for predicting early death.[6–8] However, these studies have also encountered some limitations. The models were only able to predict patients with limited survival at 30 days. It's worth noting that sCD25 (alpha chain of the soluble interleukin-2 receptor, sIL-2Rα), which is a strong prognostic factor for overall survival (OS),[9–11] was not included. Therefore, we aimed to explore the characteristics of adult patients with HLH who suffered early death (ED) and build a reliable risk model to predict ED.

Materials and Methods

Patients and Diagnostic Criteria

Our study was approved by the Medical Research Ethics Review Committee of the First Affiliated Hospital of Nanchang University (IIT2023297). All patient data were anonymised and the study adhered to the ethical principles of the Declaration of Helsinki, ensuring data confidentiality and the protection of participants' rights. Between September 2013 and July 2024, 254 adult patients with HLH met the inclusion and exclusion criteria and were admitted to the First Affiliated Hospital of Nanchang University. HLH diagnoses were conducted based on the revised diagnostic criteria stipulated in the definitive HLH-2004 protocol.[12] The HLH-2004 criteria include the following eight indicators: fever, splenomegaly, cytopenia affecting at least two lineages, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, hemophagocytosis in bone marrow, spleen, or lymph nodes, reduced/absent natural killer (NK) cell activity, and elevated levels of sCD25. We mandated the presence of at least five of the eight HLH-2004 criteria for each patient. Follow-ups commenced from the patient's admission date until 60 days or until the date of death. Methods of follow-up included telephone calls and medical record examinations. Patients lost to follow-up within 60 days, those younger than 18 years, or those with critical missing clinical data were excluded. A patient with pHLH, an 18-year-old male with a homozygous UNC13D mutation, was included in this study.

Clinical Parameters

We extracted demographic, clinical, treatment, imaging and laboratory characteristics from the patient's medical records. These characteristics included age, sex, interval from symptom onset to diagnosis/treatment, etiology, and treatment regimen. Treatment regimens included etoposide (VP-16)-based regimens (such as HLH-1994/2004, DEP) and other regimens without VP-16 (such as monotherapy with glucocorticoids, combination therapy with ruxolitinib and glucocorticoids, primary lymphoma treatment regimens (R-CHOP, etc) and supportive treatment. The following regular laboratory values were collected white blood cell (WBC) count, haemoglobin, platelet count (PLT), absolute neutrophil count, cytopenia, prothrombin time (PT), activated partial thromboplastin time (APTT), triglycerides (TG), fibrinogen (FIB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), albumin, sCD25, ferritin and NK cell activity. Note that all laboratory results were obtained within 3 days of diagnosis. We defined early mortality as death within 60 days of diagnosis.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics software, version 26.0. Continuous variables following a normal distribution are presented as the mean ± standard deviation and were analyzed using a *t*-test. For continuous variables with non-normal distributions, the median and interquartile range (IQR) are reported, and the Mann–Whitney *U*-test was employed for analysis. Categorical variables are presented as frequencies and percentages (n, %). In cases of non-normal distributions for categorical variables, Pearson's chi-squared test or Fisher's exact test was used, as appropriate. The dataset was randomly split into training (70%) and validation (30%) sets using stratified sampling via the caret package in R (version 4.3.0). Cohort characteristics of both subsets are detailed in Supplementary Table S1. The optimal cutoff values for sCD25 and EBV DNA copies were determined using receiver operating characteristic (ROC) curves, based on the maximum Youden index (sensitivity + specificity - 1). Univariate and multivariate analyses were performed using the Cox proportional hazards model with a conditional forward stepwise method. A nomogram was constructed using the rms26 package in R, version 4.3.0 (http://www.r-project.org/), and the validation cohort was used for model assessment. The model's performance was evaluated using the C-index, and a calibration curve was generated

to compare the predicted prognosis from the nomogram with the actual outcomes. Kaplan-Meier curves and Log Rank tests were utilized to compare differences in survival curves. A p-value threshold of less than 0.05 was considered statistically significant.

Results

Clinical Characteristics Between Survivors and Non-Survivors Within 60-Day

The mortality rate among patients with HLH in our study was 26.4% (67/254) within 60 days. Table 1 presents a comparison of the clinical parameters between the survivors and non-survivors. Firstly, the differences in etiology and treatment regimens between the two groups at baseline were excluded ($P = 0.476$, $P = 0.260$, respectively). The data indicated that the trigger factors in adult patients with HLH were malignancy (n = 79, 31.1%) and EBV infection (n = 66, 26.0%). About the therapeutic management of patients with HLH, 66.9% (n = 170) were primarily treated with VP-16-based regimens. In addition, 18.9% (n = 48) of patients received non-VP-16 based regimens, comprising monotherapy with glucocorticoids, combination therapy with ruxolitinib and glucocorticoids, and primary lymphoma treatment regimens (R-CHOP, etc). Furthermore, 14.2% (n = 36) of patients received supportive treatment.

Table 1 Clinical Parameters in Survivors and Non-Survivors in 60-Day in Adult Patients with HLH

Clinical Parameters	Survivors (n=187)	Non-Survivors (n=67)	*P*-value
Age (years)	50.32±15.86	55.43±16.35	0.029*
Sex (male/female)	95/93	38/29	0.246
Time from onset to diagnosis/treatment			0.471
≤15 days	36 (19.3%)	16 (23.9%)	
15–30 days	63 (33.7%)	27 (40.3%)	
30–60 days	53 (28.3%)	14 (20.9%)	
>60 days	35 (18.7%)	10 (14.9%)	
Etiology			0.476
M-HLH	58 (31.02%)	21 (31.3%)	
EBV-HLH	44 (23.53%)	22 (32.8%)	
IAHS (non-EBV)	33 (17.65%)	8 (11.9%)	
MAS	9 (4.81%)	5 (7.5%)	
FHL-3	1 (0.53%)	0	
Unknown trigger	42 (22.46%)	11 (16.4%)	
Treatment			0.260
Non-VP-16	34 (18.2%)	14 (20.9%)	
VP-16 based	130 (69.5%)	40 (59.7%)	
Supportive treatment	23 (12.3%)	13 (19.4%)	
Immunosuppression	4 (2.1%)	2 (3%)	0.500
WBC ($\times10^9$/L)	3.35 (2.04, 5.69)	2.07 (1.22, 4.26)	0.002*
Neutrophil ($\times10^9$/L)	2.1 (1.26,4.09)	1.32 (0.74, 2.57)	0.001*
Hemoglobin (g/L)	93±23.57	92±24.82	0.974
PLT ($\times10^9$/L)	80 (40, 132)	49 (23, 66)	0.000*
Cytopenia in ≥2 lineages	70 (37.4%)	41(61.2%)	0.001*
PT (s)	13 (11.8, 14.5)	12.9 (11.6, 14)	0.537
APTT (s)	32.6 (29.4, 38)	34.6 (29, 40.4)	0.250
FIB (g/L)	2.65 (1.67, 3.96)	1.84 (1.2, 2.86)	0.002*
TG (mmol/L)	2.08 (1.44, 2.99)	2.39 (1.71, 3.97)	0.040*
LDH (U/L)	578 (378.6, 975)	732.9 (407, 1367)	0.075
ALT (U/L)	45 (24.3, 96)	47 (23.75, 109.35)	0.997
AST (U/L)	69 (36.7, 133)	82.3 (50.86, 187.08)	0.039*
AKP (U/L)	112.5 (79.7, 200.5)	126 (83, 274.9)	0.123
Albumin (g/L)	30.24±5.82	28.79±5.55	0.073

(*Continued*)

Table 1 (Continued).

Clinical Parameters	Survivors (n=187)	Non-Survivors (n=67)	*P*-value
sCD25 (U/mL)	5555 (2934, 11009.64)	7482 (3436, 20800)	0.014*
Ferritin (ug/L)[+]	2225 (993.45, 6412.75)	3050 (1276.5, 10890)	0.140
EBV DNA positive	59 (31.6%)	34 (50.7%)	0.004*
EBV DNA (copies/mL)	0 (0, 1950.5)	5411 (0, 62620)	0.001*
NK cell dysfunction (< 15.11%)[+]	70 (37.4%)	20 (29.9%)	0.025*
Genetic mutation[+]	23 (37.7%)	5 (38.5%)	1.000

Notes:*Significantly different. [+]Missing partial data.

Abbreviations: M-HLH, malignancy-associated HLH; IAHS (non-EBV), non-EBV infection-associated HLH; MAS, macrophage activation syndrome; FHL-3, familial hemophagocytic lymphohistiocytosis-3; VP-16, etoposide; WBC, white blood cell; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; TG, triglyceride; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; sCD25, alpha chain of the soluble interleukin-2 receptor.

A comparison of the two groups revealed a tendency for patients in the non-survival group to be older ($P = 0.029$). The non-survival group exhibited lower levels of WBC, neutrophils, PLT, and a higher incidence of cytopenia in ≥2 lineages (61.2%) ($P = 0.002$, $P = 0.001$, $P < 0.001$, $P = 0.001$, respectively). Furthermore, elevated levels of AST, TG, and sCD25 ($P = 0.039$, $P = 0.040$, $P = 0.014$, respectively) and lower levels of FIB ($P = 0.002$) were observed in non-survivors. Notably, the non-survival group exhibited a high prevalence of EBV DNA positive (50.7%) ($P = 0.004$) and elevated EBV DNA copy numbers ($P = 0.001$).

The distinction lies in the role of ferritin, which has been identified as a prognostic indicator in patients with HLH, and did not demonstrate a statistically significant difference between the two groups ($P = 0.140$). Moreover, 37 (55.2%) cases in the non-survival group lacked data regarding NK cell activity, resulting in a greater bias in the assessment of NK cell activity.

Early Survival Rate of Patients with HLH Patients in Different Etiologies and Treatment Regimens

To investigate the differences in prognosis between the various etiologies, Kaplan-Meier survival analysis was performed. The 60-day survival rates for the respective etiologies were as follows: malignancy-associated HLH (M-HLH) (73.4%), EBV-HLH (66.7%), macrophage activation syndrome (MAS) (64.3%), non-EBV infection-associated HLH [IASH (non-EBV)] (80.5%), familial hemophagocytic lymphohistiocytosis-3 (FHL-3) (100%), and unknown (79.2%) (Figure 1A). This observation indicated that different etiologies did not exert a significant influence on early survival ($P = 0.55$). Similarly, in terms of treatment regimens, there was no significant difference in 60-day survival rates between those who received a VP-16-based regimen (76.5%) and those who received a non-VP-16 regimen (70.8%) ($P = 0.19$) (Figure 1B).

A Prognostic Model Based on sCD25 for the 60-Day Survival Rate of Adult Patients with HLH

To obtain the training and validation cohorts, a random sample (7:3 ratio) was selected from the total data set using the R. A total of 177 cases were selected for the training set and validation in a separate cohort of 77 cases. Specifically, univariate Cox regression was performed on the training cohort. In the case of parameters that are commonly employed in clinical practice, the clinical cutoff value was utilised for classification. LDH was classified using a cutoff value of 10 times the upper limit numbers (ULN), while ALT and AST were classified using a cutoff value of 5 and 10 times ULN, respectively. For uncertain upper limits, such as sCD25, ferritin, and EBV DNA copy numbers, the optimal cutoff value was determined based on the ROC curve and a simpler value was used for clinical application.

The results of the univariate Cox regression analysis indicated that the risk factors associated with 60-day mortality were WBC $<4\times 10^9$ /L ($P = 0.013$), neutrophil $<1\times 10^9$/L ($P = 0.016$), PLT $<40\times 10^9$ /L ($P = 0.002$), cytopenia in ≥2 lineages ($P = 0.008$), FIB <1 g/L ($P = 0.020$), LDH ≥10×ULN U/L ($P = 0.003$). Furthermore, the presence of sCD25

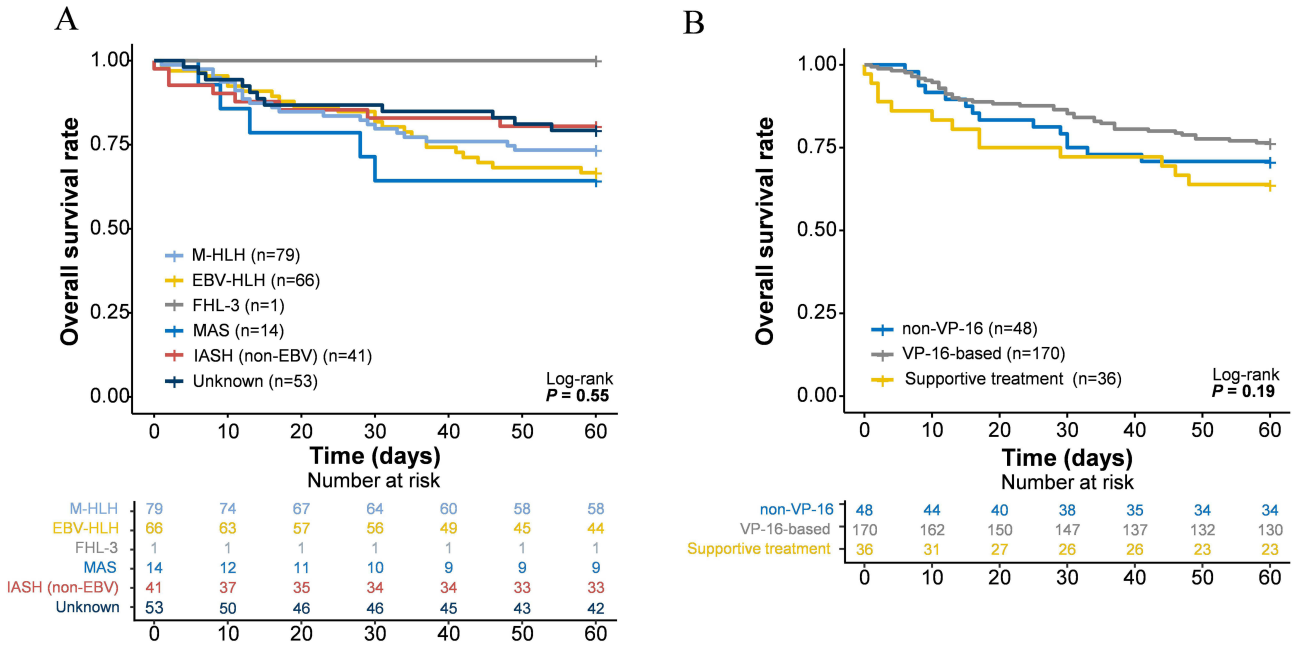

Figure 1 Early survival rate of patients with HLH in different etiologies and treatment regimens. (**A**) Survival rates across etiologies (M-HLH, EBV-HLH, FHL-3, MAS, IASH [non-EBV]) showed no significant difference ($P = 0.55$). (**B**) Survival rates did not differ among VP-16-based, non-VP-16, and supportive treatment groups ($P = 0.19$).

≥12,197.5 U/mL ($P = 0.007$) and ≥12000 U/mL ($P = 0.010$) were identified as risk factors, as were EBV DNA copies ≥ 8803.5 copies/mL ($P = 0.001$) and ≥10000 copies/mL ($P = 0.001$). (Table 2)

The Hazard Ratio (HR) values of sCD25 and EBV DNA copies were found to be comparable to the optimal cut-off value when classified at 12,000 and 10,000, respectively. To facilitate the implementation of the prognostic model in

Table 2 Univariate and Multivariate Analyses by Cox Regression in the Training Cohort

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Etiology						
M-HLH	1.355	0.571–3.119	0.505			
EBV-HLH	1.546	0.655–3.647	0.320			
IAHS (non-EBV)	0.721	0.217–2.396	0.594			
MAS	2.618	0.856–8.011	0.092			
Unknown trigger	-	-	-			
Sex (male/female)	0.991	0.562–1.749	0.976			
Age ≥60 (years)	1.075	0.599–1.928	0.809			
WBC <4 ($\times 10^9$/L)	1.529	1.092–2.141	0.013*			
Hb <90 (g/L)	1.156	0.871–1.534	0.316			
Neutrophil <1 ($\times 10^9$/L)	1.435	1.071–1.922	0.016*			
PLT <100 ($\times 10^9$/L)	1.940	1.265–2.976	0.002*	3.335	1.411–7.883	0.006*
Cytopenia in ≥2 lineages	2.180	1.222–3.890	0.008*			
PT ≥15 (s)	1.062	0.497–2.270	0.876			
APTT ≥44 (s)	1.167	0.565–2.410	0.676			
FIB <1 (g/L)	1.438	1.060–1.952	0.020*			
TG ≥1.7 (mmol/L)	1.487	0.758–2.915	0.248			
LDH ≥10×ULN (U/L)	2.464	1.351–4.494	0.003*			

(*Continued*)

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Table 2 (Continued).

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ALT (U/L)						
≥5×ULN	0.767	0.275–2.137	0.612			
≥10×ULN	0.401	0.055–2.906	0.366			
AST (U/L)						
≥5×ULN	1.337	0.680–2.627	0.399			
≥10×ULN	1.320	0.522–3.338	0.557			
AKP ≥125(U/L)	1.371	0.775–2.424	0.279			
Albumin <30 (g/L)	1.414	0.783–2.555	0.251			
NK cell dysfunction (< 15.11%)[+]	0.607	0.316–1.169	0.135			
sCD25 (U/mL)						
≥12,197.5	2.193	1.235–3.895	0.007*			
≥12,000	2.117	1.192–3.760	0.010*	1.803	1.010–3.216	0.046*
Ferritin (ug/L)[+]						
≥2000	1.347	0.732–2.481	0.338			
≥10,000	1.455	0.691–3.066	0.324			
EBV DNA copies (copies/mL)						
≥8803.5	2.703	1.521–4.802	0.001*			
≥10,000	2.581	1.445–4.607	0.001*	2.280	1.271–4.087	0.006*

Notes: *Significantly different. [+]Missing partial data.

Abbreviations: M-HLH, malignancy-associated HLH; IAHS (non-EBV), non-EBV infection-associated HLH; MAS, macrophage activation syndrome; FHL-3, familial hemophagocytic lymphohistiocytosis-3; VP-16, etoposide; WBC, white blood cell; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time, FIB, fibrinogen; TG, triglyceride; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; sCD25, alpha chain of the soluble interleukin-2 receptor.

clinical practice, a COX multivariate analysis was conducted with the inclusion of sCD25 ≥12000 U/mL and EBV DNA copies ≥10000 copies/mL as subsequent variables. A conditional forward stepwise multivariate analysis was conducted on the aforementioned variables to identify independent prognostic indicators. In conclusion, PLT <100×10^9/L (P = 0.006), sCD25 ≥12000 U/mL (P = 0.046) and EBV DNA copies ≥10000 copies/mL (P = 0.006) were identified as independent risk factors for patients death within 60 days (Table 2). Moreover, the Kaplan-Meier curves for the identified risk factors are presented in Figure 2.

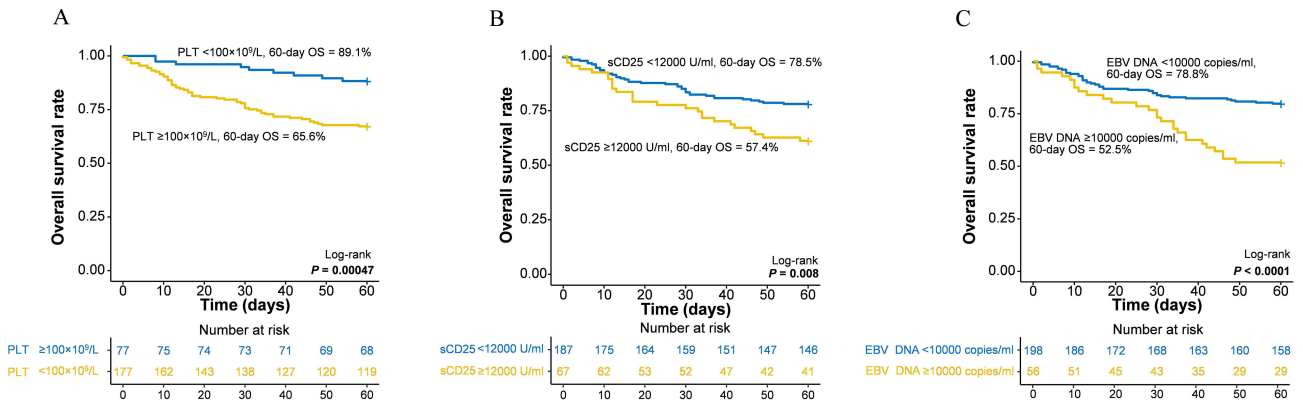

Figure 2 K-M curves of independent risk factors for early death. The survival rate in PLT <100×10^9/L and PLT ≥100×10^9/L (P = 0.00047) (**A**), sCD25 <12000 U/mL and sCD25 ≥12000 U/mL (P = 0.008) (**B**), EBV DNA copies <10000 copies/mL and EBV DNA copies ≥ 10000 copies/mL (P < 0.0001) (**C**) among 254 cases with HLH in 60-days.

The Construction, Evaluation and Validation of the Nomogram

A nomogram was constructed to develop an ED risk model for predicting 60-day survival probabilities in adult patients with HLH (Figure 3). To evaluate the predictive efficacy of the ED risk model, we examined the C-index, which yielded values of 0.698 and 0.654 for the training and validation sets, respectively. Furthermore, the calibration plots illustrated a high degree of concordance between the nomogram-predicted probability of 60-day survival and the actual observations in both the training cohort (Figure 4A) and the validation cohort (Figure 4B).

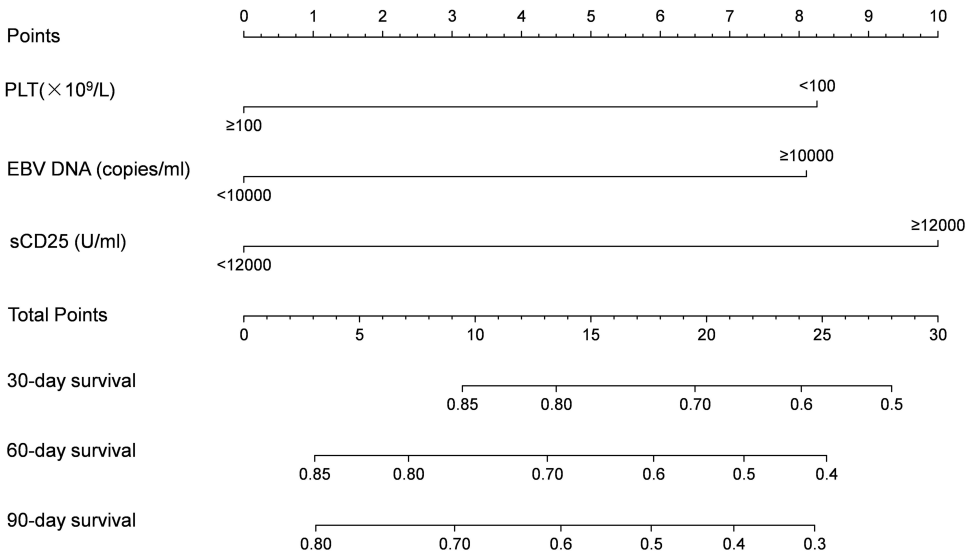

Figure 3 Nomogram for predicting the early survival rate of adult patients with HLH. The developed prognostic model and accompanying nomogram are designed to predict the early survival of adult patients with HLH. To use it, locate the scores of each variable on its respective axis, sum the points from all variables, and then ascertain the probabilities of early survival for patients based on the total points on the bottom line of the nomogram.

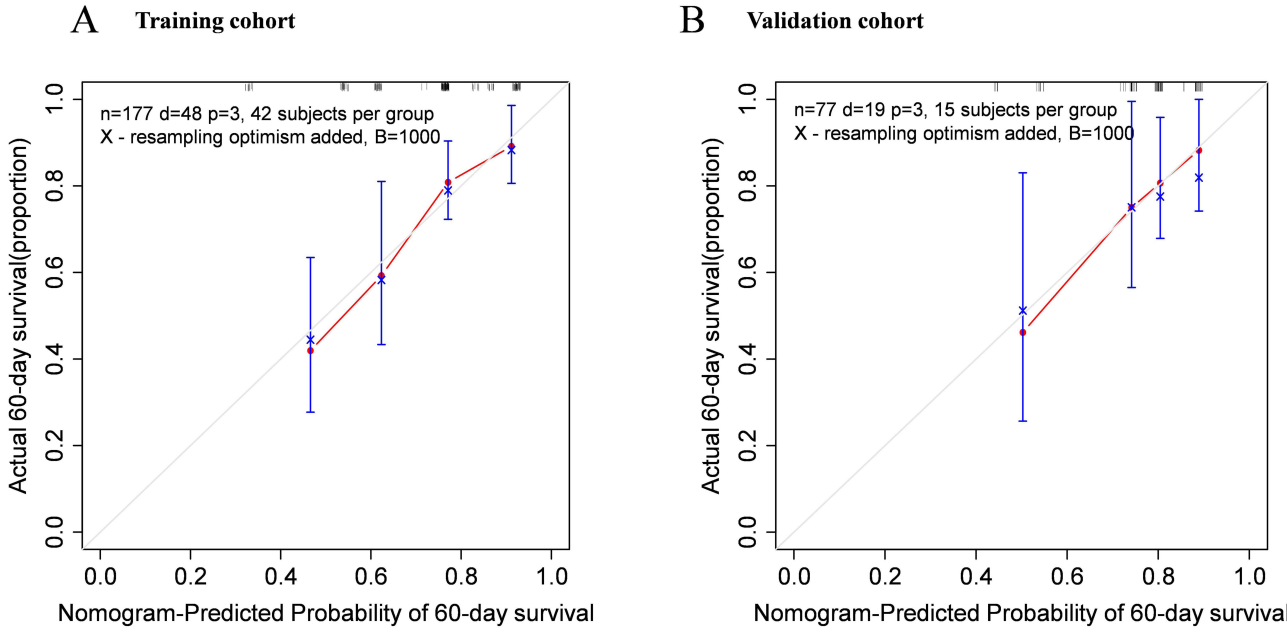

Figure 4 The calibration curve of nomogram. (**A**) The calibration curve for predicting patient survival of 60-day survival in the training cohort; (**B**) The calibration curve for predicting patient survival of 60-day survival in the validation cohort. Nomogram-predicted probability of 60-day survival is plotted on the x-axis; actual 60-day survival is plotted on the y-axis.

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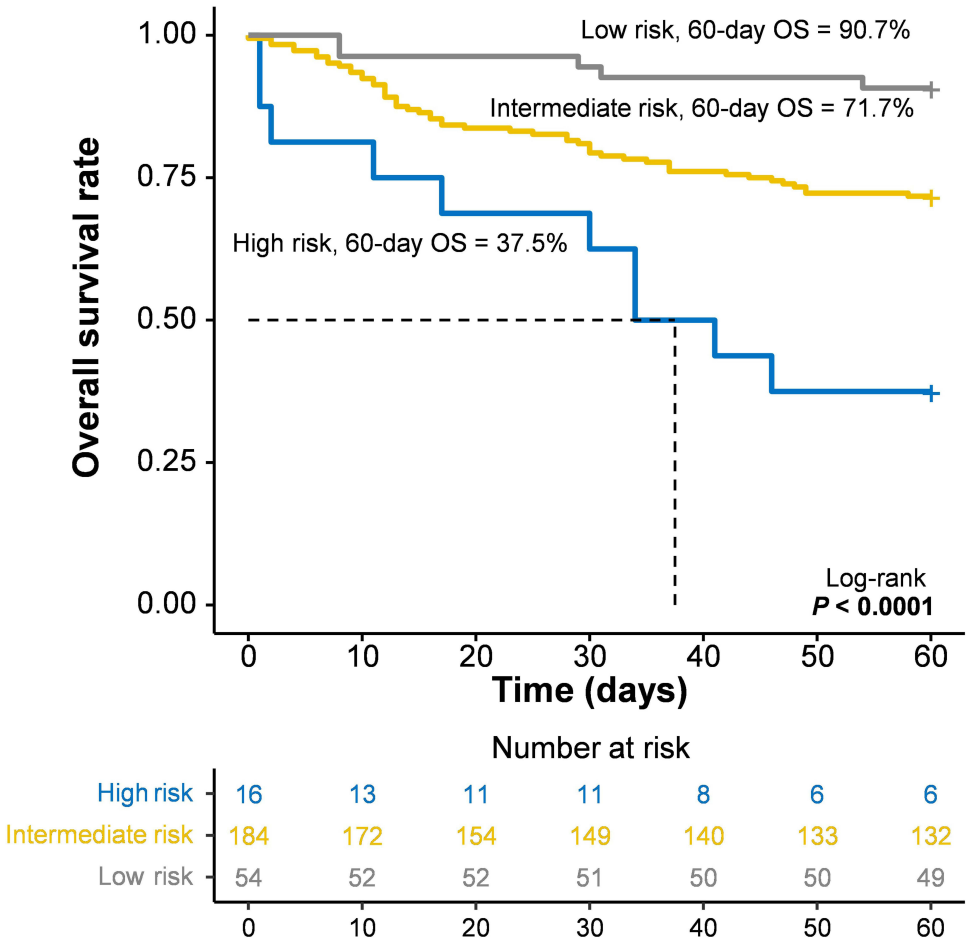

Figure 5 K-M curve of three risk groups within 60 days. The cohort of 254 patients was stratified into three distinct prognostic categories (low-risk, intermediate-risk, and high-risk groups), demonstrating significantly divergent 60-day overall survival rates of 90.7%, 71.7%, and 37.5%, respectively ($P < 0.0001$).

Given that the difference between the highest and lowest scores for each risk factor in the nomogram was less than twofold, we assigned a value of one to each factor. This approach allowed us to stratify the 254 patients into three risk groups: low-risk (n=54), intermediate-risk (n=184), and high-risk (n=16). The corresponding 60-day OS rates were 90.7%, 71.7%, and 37.5%, respectively (Figure 5) ($P < 0.0001$).

Discussion

The findings of our study indicated that malignancy and EBV infection were the most prevalent conditions among the 254 patients examined, accounting for 57.1% (n = 145) and 63.6% (n = 43) of total deaths within 60 days. Given the accelerated progression of these two predisposing factors, the mortality rate within 60 days reached 26.4% (n = 67), emphasising the necessity for the expedient identification of high-risk patients. Several early prognostic models for HLH have been presented in the literature. For instance, as early as 2015, Arca et al[6] demonstrated that in 162 patients with HLH, factors like increased age, reduced platelet count, underlying lymphoma, and the absence of etoposide in treatment are associated with poor prognosis within 30 days. Several subsequent studies have also highlighted the influencing factors of a 30-day prognosis.[7,8] However, many of these studies have limitations, particularly the lack of sCD25, which is an indicator of T cell activation.[13] Furthermore, sCD25 can identify patients with a poor prognosis in both adult patients with HLH[9] and EBV-HLH cases.[14]

The present study examined several factors, including the time from onset to diagnosis/treatment, trigger causes, treatment regimens, and laboratory results. The objective was to enhance clinical applicability and facilitate the more rapid identification of patients presenting with high inflammatory symptoms. Patients who died early exhibited characteristics such as advanced age, decreased blood cell count, low FIB, elevated TG, AST, sCD25 and EBV DNA copy

numbers. Furthermore, we introduced a 60-day survival nomogram, which demonstrated that PLT $<100\times10^9$/L (P = 0.006), sCD25 ≥12000 U/mL (P = 0.046) and EBV DNA copies ≥10000 copies/mL (P = 0.006) collectively provide an accurate forecast of the likelihood of an early outcome. The model was validated in a validation cohort, confirming the reliability of the model in predicting 60-day survival outcomes.

Thrombocytopenia emerged as another predictor of adverse prognosis in patients with HLH, a finding consistent with prior studies.[6,7,15] This condition may arise through multiple mechanisms, including impaired megakaryogenesis due to cytokine release, disseminated intravascular coagulation, or platelet depletion secondary to hypersplenism.

In China, among 1,445 reported cases of HLH, 44.01% were attributed to EBV-HLH,[16] with an overall median survival time of 135 days.[14] Elevated plasma EBV load is often indicative of active viral replication, which correlates with poor prognosis.[17] Studies have shown that patients with high plasma EBV DNA levels are at greater risk of disease recurrence.[18] Given the heightened short-term recurrence and mortality rates observed in these patients, our ED risk model provides a critical advantage by enabling rapid and precise identification of high-risk patients at the time of diagnosis—a need that has been inadequately addressed in previous reports.

Ferritin, which is secreted by macrophages via non-traditional lysosomal pathways, is frequently regarded as a marker for macrophage activation.[19,20] The present study has demonstrated that ferritin is an ineffective marker for identifying patients at high risk in the early stages of illness. Similarly, the report by Abou et al[21] emphasised that an increase in ferritin levels is linked to an elevated risk of early mortality, rather than the level on admission. The level of ferritin index (the percentage reduction in serum ferritin from admission to discharge) can predict the 6-month survival rate in adult patients with HLH.[22] Furthermore, the combination of sCD25 and ferritin also can provide a more accurate identification of patients with a poor prognosis, including those with non-HLH, M-HLH and high inflammatory status.[10] However, these studies lacked the capacity to identify high-risk patients at an early stage.

Some limitations in this study should be considered. The retrospective design may introduce selection bias. Most deaths occurred outside of hospitals, making it difficult to determine the exact causes of death. Additionally, sCD25 levels are not readily available in routine clinical settings, which may hinder the broader application of the findings. Furthermore, external validation is required before the results can be applied in clinical practice.

Conclusion

Collectively, the ED risk model has a substantial patient population with HLH and is somewhat innovative, highlighting the benefits of identifying elevated inflammatory states. The model is capable of more accurately identifying subgroups at an elevated risk of early mortality, which may assist in clinical decision-making for adult patients with HLH.

Data Sharing Statement

The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Ethics Statement

The present study was approved by the Medical Research Ethics Review Committee of the First Affiliated Hospital of Nanchang University (IIT2023297). The need for consent was waived due to the retrospective nature of the study. All patient data were anonymised and the study adhered to the ethical principles of the Declaration of Helsinki, ensuring data confidentiality and the protection of participants' rights.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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