BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

COX Regression Analysis and Mortality Risk Prediction Model of 85 Adult Patients with Secondary Hemophagocytic Lymphohistiocytosis

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Abstract

Aims/Background Secondary hemophagocytic lymphohistiocytosis (sHLH) is a rare, rapidly progressive and highly lethal disease. This retrospective cohort study aims to analyze the factors influencing the mortality risk in adult patients with sHLH, which are instrumental to improving our understanding of the high mortality risks associated with sHLH.

Methods This study included 85 patients diagnosed with sHLH who were admitted and treated in the Department of Emergency, Peking University People's Hospital between April 2015 and July 2023. Participants were classified based on prognosis into two groups: the death group and the survival group. We collected demographic data, routine blood tests, comprehensive biochemical profiles, coagulation analyses, serum ferritin levels, natural killer (NK) cell counts, soluble interleukin-2 receptor (sCD25) levels, and potential etiological factors upon admission. The mortality risk factors influencing the prognosis of sHLH were analyzed with univariate and multivariate COX regression. Additionally, a mortality risk prediction model was established, and its accuracy was validated and optimized using the concordance index (C-index), time-dependent receiver operating characteristic (ROC) curve, calibration curves and clinical decision curve analysis (DCA).

Results A total of 85 patients were included in this study, the male-to-female ratio is 1:1.4. The median age at diagnosis of sHLH was 56.00 (33.00–69.00) years. Clinical symptoms were atypical, with fever being the most prevalent symptom (81 cases, 95.3%), followed by disturbance of consciousness (10 cases, 11.8%). Univariate COX analysis and Multivariate COX regression analysis revealed that age (hazard ratio (HR) [95% confidence interval (CI)], 1.098 [1.025–1.177], $p = 0.008$), Alanine transaminase (ALT) (HR [95% CI], 1.016 [1.001–1.031], $p = 0.034$), Aspartate transaminase (AST) (HR [95% CI], 1.005 [1.001–1.008], $p = 0.004$), and Troponin I (TNI) levels (HR [95% CI], 1.196 [1.011–1.414], $p = 0.037$) were independent risk factors affecting prognosis. Specifically, sHLH patients aged ≥63.5 years (sensitivity 82.8%, specificity 85.7%), with AST levels ≥111 U/L (sensitivity 82.8%, specificity 82.1%), ALT ≥41 U/L (sensitivity 58.6%, specificity 64.3%) and TNI levels ≥2.15 ng/mL (sensitivity 62.1%, specificity 100%), faced a higher risk of mortality. We established a mortality risk prediction model for sHLH patients, which yielded a C-index of 0.848 (0.773–0.901), indicating strong agreement between predicted and observed outcomes. The ROC curves of the 28-day, 60-day, and 90-day mortality risk prediction model for sHLH patients were drawn, and the results showed that the 28-day, 60-day, and 90-day area under the curve (AUC) were 0.900 (0.829–0.971), 0.940 (0.882–0.998), and 0.930 (0.874–0.986), respectively. The predictive effect of the prediction model is satisfactory. Additionally, the clinical decision curve analysis for 28, 60 and 90 days in sHLH patients indicated that the net benefit of the nomogram model was higher than that line of extremes models (treat all and treat none).

Conclusion Patients with sHLH have frequently atypical clinical presentation, with early death risk and notably elevated mortality rate. Independent risk factors influencing mortality risk in sHLH patients include age ≥63.5 years, AST ≥111 U/L, ALT ≥41 U/L, and TNI ≥2.15 ng/mL. With high accuracy and efficacy, the risk prediction model constructed can facilitate timely identification of sHLH patients at elevated risk of mortality, which is critical for optimizing clinical interventions.

Key words: secondary hemophagocytic lymphohistiocytosis; risk of death; COX regression; risk prediction model

Submitted: 16 October 2024 Revised: 25 November 2024 Accepted: 27 November 2024

How to cite this article:
Wang K, Hu M, Zhu J, Wang W. COX Regression Analysis and Mortality Risk Prediction Model of 85 Adult Patients with Secondary Hemophagocytic Lymphohistiocytosis. Br J Hosp Med. 2024.
https://doi.org/10.12968/hmed.2024.0794

Introduction

Hemophagocytic syndrome (HPS), commonly referred to as hemophagocytic lymphohistiocytosis (HLH), is a rare but life-threatening disorder, which is classified into primary and secondary variants, distinguished by the presence or absence of HLH-related genetic abnormalities. Initially reported by paediatrician Scott (1939), secondary hemophagocytic lymphohistiocytosis (sHLH) was first recognized as a histiocytic disorder of the marrow and spleen. The condition was officially designated as "secondary hematophagocytic syndrome" by the Histiocyte Society in 1991 (Henter et al, 1991; Scott, 1939). sHLH is a rapidly progressive disease, with an estimated annual incidence of 1 in 800,000 adults and 1–10 in 1,000,000 children across Sweden, Italy, and the United States. The main clinical manifestations include fever, organomegaly, pancytopenia, abnormal coagulation function, hyperferritinemia, and hemophagocytic phenomena observed in bone marrow and other tissues. Patients not receiving treatments often have a median survival period of less than 2 months (Al-Samkari and Berliner, 2018; Vavassori et al, 2021). sHLH is more prevalent in adult populations, with infections, autoimmune disorders, and malignancies being common etiological contributors. While relatively infrequent in clinical practice, sHLH often presents with acute and rapid onset, leading to a high mortality rate if not diagnosed and treated expeditiously.

Currently, there is a paucity of research concerning adult sHLH, particularly regarding the factors influencing mortality risk. In a study of 126 patients with sHLH, a multivariate regression analysis showed that lymphocyte count $<0.45 \times 10^9$/L, activated partial thromboplastin time (APTT) $\geq$39.7 s and Albumin (ALB) $<$25.9 g/L were independent risk factors for death within 30 days in sHLH patients; however, a nomogram model established based on these three risk factors had a concordance index (C-index) of only 0.683, indicating relatively poor accuracy of the model (Zhu et al, 2023). A multivariate analysis conducted in another study of 162 adult patients with sHLH showed that male sex, APTT $>$36 s, lactate dehydrogenase (LDH) $>$1000 U/L, and C-reactive protein (CRP) $>$100 mg/L were the independent risk factors for the prognosis of HLH, but a valid prediction model was not established (Zhang et al, 2022). Therefore, this study was conducted to dissect the high mortality risk of sHLH by systematically analyzing the relevant factors contributing to mortality in the adult patient group.

Methods

Study Participants

The participants included in this study were patients diagnosed with sHLH at the Department of Emergency, Peking University People's Hospital from April 2015 and July 2023. The inclusion criteria adhered to the HLH diagnostic standards established by the International Histiocyte Society in 2004 (Henter et al, 2007), as detailed below:

(i) A molecular diagnosis consistent with HLH.

(ii) Fulfillment of five or more of the following eight criteria:

• Fever: A body temperature exceeding 38.5 °C, persisting for more than 7 days.

• Splenomegaly.

• Cytopenia is characterized by haemoglobin $<$90 g/L, platelets $<100 \times 10^9$/L, and neutrophils $<1.0 \times 10^9$/L, which is not attributed to impaired bone marrow hematopoietic function.

• Hypertriglyceridemia and/or hypofibrinogenemia: Triglycerides $>$3 mmol/L and fibrinogen $<$1.5 g/L.

• Hemophagocytic phenomena detected in bone marrow, spleen, liver, or lymph nodes.

• Reduced or absent natural killer (NK) cell function.

• Ferritin levels $\geq$500 μg/L.

• Elevated soluble interleukin-2 receptor (sCD25) levels: $\geq$2400 U/mL.

After excluding three patients under the age of 18 and two individuals with incomplete clinical data, the sHLH patients recruited underwent secondary aetiology or genetic testing for primary sHLH exclusion. A total of 85 patients with secondary HLH were ultimately enrolled in this study. This research received approval from the Ethics Committee of Peking University People's Hospital (No. 2024PHB066-001), and informed consent to participate was obtained from patients or their relatives. This study was conducted in adherence with the guidelines outlined in the Declaration of Helsinki.

Methods and Statistical Analysis

In this study, the outcome data of the patients were obtained through follow-up: the survival time of the enrolled sHLH patients was monitored from their initial visit until either their demise, loss to follow-up, or the last recorded follow-up time, with a maximum follow-up duration of 90 days. Follow-up procedures included medical records review, notification to patients and/or family members through letters, telephone interviews, and direct inquiries. The follow-up period concluded on 30 July 2023, and was conducted by professionally trained healthcare personnel. Patients diagnosed with sHLH were stratified into two groups based on their follow-up outcomes: those who succumbed to the condition and those who survived. The research data encompassed several key components, including baseline characteristics (gender, age), clinical features, and laboratory data (routine blood test, liver function index, renal function index, heart function index, coagulation function index, blood lipid and other laboratory indicators). The aforementioned data were acquired through a comprehensive examination of the patient's medical records and meticulous collection of laboratory data.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), GraphPad Prism version 10.3.0 for Windows (GraphPad Software, Boston, MA, USA), and R4.4.1 (https://www.r-project.org/). Data with a normal distribution are denoted as mean ± standard deviation, while non-normal distribution data are represented by median and interquartile range (M [Q1, Q3]). Categorical data are expressed as percentages (%). The analysis included various statistical methods such as independent sample *t*-tests,

nonparametric rank sum tests, and chi-square tests for group comparisons, Fisher's precision probability test was used when the sample size was n < 40 or the number of cases with expected frequency T < 1 or expected frequency <5 exceeded 20%. Survival curves were plotted using the Kaplan-Meier method, and the log-rank or Breslow test was applied to analyze survival time and compare prognostic factors among groups. The COX regression model was employed for univariate and multivariate survival analyses, while the R4.4.1 software (https://www.r-project.org/) was utilized to construct a death risk nomogram model. The discriminative ability of the model was evaluated using the C-index, and internal validation was performed through 100 repeated samplings using the bootstrap self-sampling method. Additionally, the calibration curve and receiver operating characteristics (ROC) curve were plotted to assess the accuracy of the model. Furthermore, the clinical decision curve analysis (DCA) was employed to evaluate the utility of the model. Calibration curve, ROC curve and DCA curve were drawn using the R survive package (https://www.r-project.org/). Statistical significance was defined at $p < 0.05$.

Results

Baseline Clinical Characteristics

A total of 85 patients were enrolled in this study, consisting of 35 males (41.2%) and 50 females (58.8%). The median follow-up time of all patients was 56 ± 21 days. The mean age at diagnosis of sHLH was 56.00 (33–69) years. Clinical symptoms were atypical, with the most prevalent symptom being fever observed in 81 patients (95.3%), followed by altered consciousness, which occurred in 10 patients (11.8%). The most commonly reported comorbidities included hypertension in 16 patients (18.8%), diabetes mellitus reported in 15 patients (17.6%), and coronary atherosclerotic heart disease (CHD) reported in 8 patients (9.4%). In terms of aetiology, the number of subjects in the tumour group was 31 (36.47%), immunity group 39 (45.88%), infection group 13 (15.29%), and unknown group 2 (2.35%) (Table 1).

Results of Univariate Analysis of sHLH

In this study, a total of 85 patients were categorized into two groups based on their prognoses at the final follow-up: the death group, which included 25 patients (29.4%), and the survival group, consisting of 60 patients (70.6%). Univariate analysis of baseline characteristics and laboratory parameters between the two groups indicated that the subjects in the death group were significantly older than those in the survival group ($p < 0.05$). Additionally, levels of Aspartate transaminase (AST), Troponin I (TNI), blood urea nitrogen (BUN), and brain natriuretic peptide (BNP) were markedly elevated in the death group ($p < 0.05$), whereas lymphocyte (LY) (%) and low-density lipoprotein (LDL) levels were significantly reduced ($p < 0.05$). Regarding aetiology, tumour-related sHLH exhibited a higher mortality rate compared to sHLH attributed to other causes ($p < 0.05$) (Table 2).

Table 1. Baseline characteristics and various clinical indicators of the patients.

Variables	Patients enrolled (n = 85)
Gender	
Male	35 (41.2%)
Female	50 (58.8%)
Age (years)	56 (33–69)
Past medical history	
Hypertension	16 (18.8%)
Diabetes	15 (17.6%)
CHD	8 (9.4%)
Clinical symptoms	
Fever	81 (95.3%)
Disturbance of consciousness	10 (11.8%)
WBC ($\times 10^9$ L)	4.07 (1.55–7.98)
LY (%)	17.10 (8.75–31.45)
NE (%)	71.00 (56.25–84.10)
HGB (g/L)	92.00 (69.00–108.00)
PLT ($\times 10^9$/L)	55.00 (24.00–107.50)
MPV (fL)	10.75 (9.50–11.70)
ALB (g/L)	29.20 (25.70–32.60)
ALT (U/L)	33.00 (19.00–83.00)
AST (U/L)	81.00 (32.5–245.00)
LDH (U/L)	600.00 (348.50–1166.00)
CK (U/L)	43.00 (21.00–121.00)
HPP	15 (17.64%)
PT (s)	12.90 (11.25–15.10)
APTT (s)	31.60 (28.30–36.10)
D-Dimer (ng/mL)	2275.00 (721.00–5510.00)
BUN (mmol/L)	6.52 (4.22–11.92)
CR (μmol/L)	73.00 (58.00–114.00)
TC (mmol/L)	2.73 (2.30–3.87)
TG (mmol/L)	2.10 (1.29–3.64)
HDL (mmol/L)	0.63 (0.38–0.89)
LDL (mmol/L)	1.44 (0.96–2.26)
TNI (ng/mL)	0.023 (0.007–0.412)
BNP (pg/mL)	117.00 (42.00–383.50)
PCT (ng/mL)	0.68 (0.23–2.39)
CRP (mg/L)	48.50 (21.58–107.98)
Ferritin (ng/mL)	7488.00 (1999.00–18,747.00)
Activity of NK cells (%)	13.92 (11.85–15.99)
sCD25 (pg/mL)	20,020.00 (12,090.75–39,901.75)
Etiological grouping	
Tumour group	31 (36.47%)
Immunity group	39 (45.88%)
Infection group	13 (15.29%)
Unknown group	2 (2.35%)

Table 1. Continued.

Variables	Patients enrolled (n = 85)
Therapeutic regimen	
Standard therapeutic doses of dexamethasone	81 (95.29%)
Human gamma globulin	68 (80.00%)
Etoposide	16 (18.82%)
Rituximab	21 (24.71%)

WBC, White blood cell; LY, lymphocyte; NE, Neutrophile granulocyte; HGB, haemoglobin; PLT, platelets; MPV, Mean platelet volume; ALB, Albumin; ALT, Alanine transaminase; AST, Aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, Activated partial thromboplastin time; CR, Creatinine; BUN, blood urea nitrogen; TC, Total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TNI, Troponin I; BNP, brain natriuretic peptide; HPP, Hemophagocytosis phenomenon; CHD, coronary atherosclerotic heart disease; PCT, procalcitonin; CRP, C-reactive protein; sCD25, soluble interleukin-2 receptor.

Multivariate COX Regression Analysis of sHLH

Multivariate COX Regression Analysis Results

The univariate analysis of this study was based on the comparison between the death group and the survival group, which did not involve the time variable. In our data analysis workflow, both univariate and multivariate COX regression analyses were first conducted, and then, a prediction model was established based on the results of the multivariate COX regression analysis. We also conducted univariate COX regression analysis of baseline characteristics and laboratory parameters for the two groups, which revealed that the age of patients, clinical manifestation of disturbance of consciousness (DOC), levels of ALT, AST, TNI, BNP, creatine kinase (CK), lactate dehydrogenase (LDH), prothrombin time (PT), procalcitonin (PCT), and LDL were prognostic factors of sHLH patients ($p < 0.05$) (Table 3). COX regression analysis was conducted to identify independent risk factors influencing patient mortality among the variables identified in the univariate screening. The findings indicated that age, ALT, AST, and TNI levels were significant independent risk factors affecting the prognosis of patients with sHLH (Table 4). Specifically, through the ROC curve, we identified age ≥63.5 years (sensitivity 82.8%, specificity 85.7%), with AST levels ≥111 U/L (sensitivity 82.8%, specificity 82.1%), ALT ≥41 U/L (sensitivity 58.6%, specificity 64.3%) and TNI levels ≥2.15 ng/mL (sensitivity 62.1%, specificity 100%) as the independent risk factors for death in patients with hemophagocytic syndrome (Figs. 1,2 and Table 5).

Results of Kaplan-Meier Survival Analysis

Survival curves for multiple factors of patients were plotted using the Kaplan-Meier survival analysis (Fig. 3). The age, ALT, AST, and TNI of sHLH patients were classified as "≥cutoff value" and "<cutoff value" groups based on the cutoff values of the ROC curve. Through the Kaplan-Meier survival analysis and log-rank

Table 2. Univariate comparison between death group and survival group of sHLH.

Variables	Death group	Survival group	Statistical value	*p*-value
Gender			$\chi^2 = 1.713$	0.191
Male	13	22		
Female	12	38		
Age (years)	71.00 (64.00–80.00)	39.5 (29.00–56.75)	Z = –5.888	<0.001▲
Past medical history				
Hypertension	6	10	$\chi^2 = 0.621$	0.431
Diabetes	6	9	$\chi^2 = 0.984$	0.321
CHD	3	5	$\chi^2 = 0.278$	0.598
Clinical symptoms				
Fever	23	58	$\chi^2 = 0.132$	0.716
Disturbance of consciousness	3	7		1.000*
WBC ($\times 10^9$ L)	4.36 (1.40–10.15)	2.97 (1.43–7.72)	Z = –0.542	0.588
LY (%)	13.60 (5.90–23.25)	20.75 (12.05–39.18)	Z = –1.973	0.048▲
NE (%)	71.40 (66.95–88.00)	68.85 (47.13–78.83)	Z = –1.513	0.130
HGB (g/L)	77.00 (67.50–110.00)	93.50 (69.75–108.00)	Z = –0.701	0.484
PLT ($\times 10^9$/L)	47.00 (26.50–66.50)	65.50 (23.25–134.00)	Z = –0.915	0.360
MPV (fL)	11.15 (9.63–11.88)	10.65 (9.33–11.48)	Z = –0.895	0.371
ALB (g/L)	27.50 (21.90–31.85)	30.30 (26.43–34.00)	Z = –1.748	0.080
ALT (U/L)	50.00 (23.00–170.50)	29.00 (17.00–69.00)	Z = –1.948	0.051
AST (U/L)	423.00 (119.00–680.00)	42.00 (28.25–92.50)	Z = –5.025	<0.001▲
LDH (U/L)	845.00 (388.00–1373.00)	498.00 (325.50–970.75)	Z = –1.421	0.155
CK (U/L)	68.00 (33.00–152.50)	35.00 (19.50–135.50)	Z = –1.808	0.071
HPP	2	13	$\chi^2 = 1.425$	0.233
PT (s)	14.50 (11.50–17.00)	12.80 (11.20–14.08)	Z = –1.912	0.056
APTT (s)	32.60 (29.90–39.65)	31.60 (28.70–36.00)	Z = –1.034	0.301
D-Dimer (ng/mL)	2285.00 (808.00–5258.00)	1574.00 (663.00–5393.00)	Z = –0.389	0.697
BUN (mmol/L)	11.70 (6.34–15.23)	4.92 (3.80–8.39)	Z = –3.514	<0.001▲
CR (μmol/L)	73.00 (58.00–114.00)	65.00 (51.00–98.00)	Z = –1.371	0.170
TC (mmol/L)	2.73 (2.30–3.87)	3.12 (2.47–3.97)	Z = –0.869	0.385
TG (mmol/L)	2.10 (1.29–3.64)	2.44 (1.41–3.44)	Z = 0.005	0.996
HDL (mmol/L)	0.63 (0.38 –0.89)	0.68 (0.42–0.86)	Z = –0.148	0.882
LDL (mmol/L)	1.06 (0.69–1.45)	1.69 (1.02–2.43)	Z = –2.802	0.005▲
TNI (ng/mL)	5.05 (0.28–8.43)	0.010 (0.00–0.31)	Z = –5.760	<0.001▲
BNP (pg/mL)	267.75 (87.00–507.75)	79.00 (31.00–301.15)	Z = –2.306	0.021▲
Ferritin (ng/mL)	5039.00 (2201.00–13,648.50)	8731.50 (2232.25–21,465.25)	Z = –1.033	0.302
PCT (ng/mL)	1.76 (0.88–14.60)	0.46 (0.178–1.71)	Z = –4.187	<0.001▲
CRP (mg/L)	77.60 (30.80–120.35)	43.47 (11.81–97.50)	Z = –1.586	0.113

Table 2. Continued.

Variables	Death group	Survival group	Statistical value	*p*-value
Activity of NK cells (%)	13.21 (10.50–16.05)	14.05 (12.47–15.99)	Z = –1.201	0.230
sCD25 (pg/mL)	22,885.00 (15,050.50–43,900.50)	19,875.50 (11,750.75–37,996.00)	Z = –1.118	0.264
Etiological grouping	25	60		0.031▲*
Tumour group	15	16	$\chi^2 = 7.425^a$	0.009^a▲
Immunity group	7	32		0.697^b*
Infection group	3	10	$\chi^2 = 2.427^c$	0.182^c
Unknown group	0	2		
Therapeutic regimen				
Standard therapeutic doses of dexamethasone	23	58	$\chi^2 = 0.132$	0.716
Human gamma globulin	18	50	$\chi^2 = 1.417$	0.234
Etoposide	6	10	$\chi^2 = 0.234$	0.629
Rituximab	8	13	$\chi^2 = 1.013$	0.314

▲Statistically significant difference.
* Fisher's precision probability test.
[a] Pairwise comparisons between tumour group and immunity group.
[b] Pairwise comparisons between immunity group and infection group.
[c] Pairwise comparisons between tumour group and infection group.
WBC, White blood cell; LY, lymphocyte; NE, Neutrophile granulocyte; HGB, haemoglobin; MPV, Mean platelet volume; ALB, Albumin; ALT, Alanine transaminase; AST, Aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; CR, Creatinine; BUN, blood urea nitrogen; TC, Total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TNI, Troponin I; BNP, brain natriuretic peptide; HPP, Hemophagocytosis phenomenon; sHLH, secondary hemophagocytic lymphohistiocytosis.

test, a significant difference was observed in the cumulative survival rates between the two groups ($p < 0.001$).

Establishment and Evaluation of Mortality Risk Prediction Model (Nomogram)

Based on the results of the COX regression analysis, a nomogram for the sHLH-related predictive model was constructed (Fig. 4). This nomogram enables the estimation of overall survival rates of sHLH patients at 28, 60, and 90 days after disease onset. Each influencing factor corresponds to a specific point value; a vertical line is drawn from this point to the score axis to determine the score. The scores for each variable are then summed to obtain a total score, which is marked on the total score axis. A vertical line is drawn down to the survival axis to derive the survival probability of the patient at 28, 60, and 90 days post-onset.

The early prediction and assessment of mortality risk factors in sHLH patients are crucial for informed clinical decision-making. The C-index of the model is 0.848 (0.773–0.901), indicating strong predictive accuracy. The calibration curve shows good alignment with the ideal curve, suggesting high accuracy for the model (Fig. 5).

Table 3. Univariate and multivariate COX regression analysis of sHLH.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender	1.995 (0.095–4.168)	0.066		
Age (years)	1.068 (1.041–1.095)	<0.001▲	1.098 (1.025–1.177)	0.008▲
Past medical history				
Hypertension	1.155 (1.041–1.095)	0.757		
Diabetes	1.190 (0.508–2.790)	0.688		
CHD	2.355 (0.889–6.239)	0.085		
Clinical symptoms				
Fever	1.056 (0.143–7.813)	0.958		
Disturbance of consciousness	2.714 (1.241–5.937)	0.012▲	1.311 (0.210–8.171)	0.772
WBC ($\times 10^9$ L)	1.000 (0.974–1.027)	0.993		
LY (%)	0.982 (0.961–1.003)	0.096		
NE (%)	1.020 (1.000–1.040)	0.054		
HGB (g/L)	0.993 (0.978–1.008)	0.372		
PLT ($\times 10^9$/L)	0.996 (0.991–1.002)	0.207		
MPV (fL)	1.117 (0.897–1.391)	0.322		
PCT (ng/mL)	1.021 (1.007–1.036)	0.004▲	1.002 (0.955–1.051)	0.935
CRP (mg/L)	1.001 (0.996–1.036)	0.623		
ESR (mm/60 min)	0.998 (0.983–1.013)	0.796		
ALB (g/L)	0.955 (0.888–1.027)	0.211		
ALT (U/L)	1.002 (1.000–1.004)	0.041▲	1.016 (1.001–1.031)	0.034▲
AST (U/L)	1.001 (1.001–1.002)	<0.001▲	1.005 (1.001–1.008)	0.004▲
LDH (U/L)	1.000 (1.000–1.001)	0.001▲	1.000 (1.000–1.001)	0.178
CK (U/L)	1.001 (1.000–1.001)	0.001▲	0.989 (0.959–1.020)	0.477
HPP	0.998 (0.983–1.013)	0.794		
PT (s)	1.036 (1.003–1.070)	0.035▲	0.911 (0.815–1.017)	0.098
APTT (s)	0.990 (0.964–1.017)	0.458		
FDP (ng/mL)	1.002 (0.997–1.006)	0.417		
D-Dimer (ng/mL)	1.000 (1.000–1.000)	0.126		
BUN (mmol/L)	1.019 (0.991–1.048)	0.188		
CR (μmol/L)	1.000 (0.996–1.004)	0.967		
TC (mmol/L)	0.857 (0.659–1.115)	0.251		
TG (mmol/L)	0.981 (0.786–1.226)	0.868		
HDL (mmol/L)	1.138 (0.372–3.479)	0.821		
LDL (mmol/L)	0.580 (0.385–0.874)	0.009▲	0.721 (0.407–1.280)	0.264
TNI (ng/mL)	1.135 (1.080–1.192)	<0.001▲	1.196 (1.011–1.414)	0.037▲
BNP (pg/mL)	1.001 (1.000–1.002)	0.045▲	1.000 (0.999–1.000)	0.261
Ferritin (ng/mL)	1.000 (1.000–1.000)	0.760		
Activity of NK cells (%)	0.924 (0.795–1.074)	0.301		
sCD25 (pg/mL)	1.000 (1.000–1.000)	0.689		
Etiological grouping				
Tumour group	3.356 (0.020–7.564)	0.365		

Table 3. Continued.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Immunity group	1.081 (0.360–3.215)	0.760		
Infection group	1.231 (0.506–1.732)	0.321		
Unknown group	2.521 (0.120–3.123)	0.412		
Therapeutic regimen				
Standard therapeutic doses of dexamethasone	1.214 (0.583–1.191)	0.522		
Human immune globulin	0.877 (0.697–1.091)	0.215		
Etoposide	1.231 (0.854–1.451)	0.532		
Rituximab	0.731 (0.654–1.051)	0.342		

▲Statistically significant difference.
WBC, White blood cell; LY, lymphocyte; NE, Neutrophile granulocyte; HGB, haemoglobin; MPV, Mean platelet volume; ALB, Albumin; ALT, Alanine transaminase; AST, Aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, Activated partial thromboplastin time; CR, Creatinine; BUN, blood urea nitrogen; TC, Total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TNI, Troponin I; BNP, brain natriuretic peptide; HPP, Hemophagocytosis phenomenon; CHD, coronary atherosclerotic heart disease; CRP, C-reactive protein; PCT, procalcitonin; ESR, Erythrocyte sedimentation rate; sCD25, soluble interleukin-2 receptor; CI, confidence interval; HR, hazard ratio.

The ROC curves of prediction model for mortality risk at 28, 60 and 90 days in sHLH patients were drawn, showing that the 28-day, 60-day, and 90-day area under the curve (AUC) (95% CI) were 0.900 (0.829–0.971), 0.940 (0.882–0.998), and 0.930 (0.874–0.986), respectively. The predictive effect of the prediction model is satisfactory (Fig. 6).

DCA was also conducted to confirm the predictiveness of the nomogram. The results indicated that the net benefit of the nomogram model outweighed that of the extremes models (treat all and treat none) over a wide range of threshold probabilities in both the derivation and validation cohorts (Fig. 7), suggesting that the superior clinical utility of the nomogram in the present study was generalizable.

Discussion

The low overall incidence and the less specific clinical symptoms of HLH pose challenges for early clinical diagnosis. This study retrospectively analyzed 85 cases of sHLH diagnosed at our institution over a 9-year period from 2015 to 2023. The most common clinical manifestations we observed from this sample were fever, disturbances of consciousness, hepatosplenomegaly, and multiple organ failure.

In other studies, patients with macrophage activation syndrome (MAS) group received steroids, cyclosporine, and interleukin (IL)-2, while those with tumour primarily underwent chemotherapy and received janus kinase (JAK) inhibitors and rituximab (Birndt et al, 2020; Chinn et al, 2018; Kalinichenko et al, 2021; Volkmer et al, 2019). For individuals with other etiologies, the main treatment strat-

Table 4. Multivariate COX regression analysis of sHLH.

Observation index	B	SE	Wald χ^2	*p*-value	HR (95% CI)
Age (years)	0.094	0.035	6.987	0.008▲	1.098 (1.025–1.177)
ALT (U/L)	0.016	0.008	4.477	0.034▲	1.016 (1.001–1.031)
AST (U/L)	0.005	0.002	8.101	0.004▲	1.005 (1.001–1.008)
LDL (mmol/L)	–0.327	0.292	1.248	0.264	0.721 (0.407–1.280)
TNI (ng/mL)	0.179	0.086	4.343	0.037▲	1.196 (1.011–1.414)
BNP (pg/mL)	0.000	0.000	1.263	0.261	1.000 (0.999–1.000)
PCT (ng/mL)	0.002	0.024	0.007	0.935	1.002 (0.955–1.051)
PT (s)	–0.094	0.057	2.734	0.098	0.911 (0.815–1.017)
LDH (U/L)	0.000	0.000	1.811	0.178	1.000 (1.000–1.001)
CK (U/L)	–0.011	0.016	0.506	0.477	0.989 (0.959–1.020)
DOC	0.271	0.934	0.084	0.772	1.311 (0.210–8.171)

▲Statistically significant difference.

ALT, Alanine transaminase; AST, Aspartate transaminase; LDL, low-density lipoprotein; TNI, Troponin I; BNP, brain natriuretic peptide; PCT, procalcitonin; PT, prothrombin time; LDH, lactate dehydrogenase; CK, creatine kinase; DOC, disturbance of consciousness; SE, standard error.

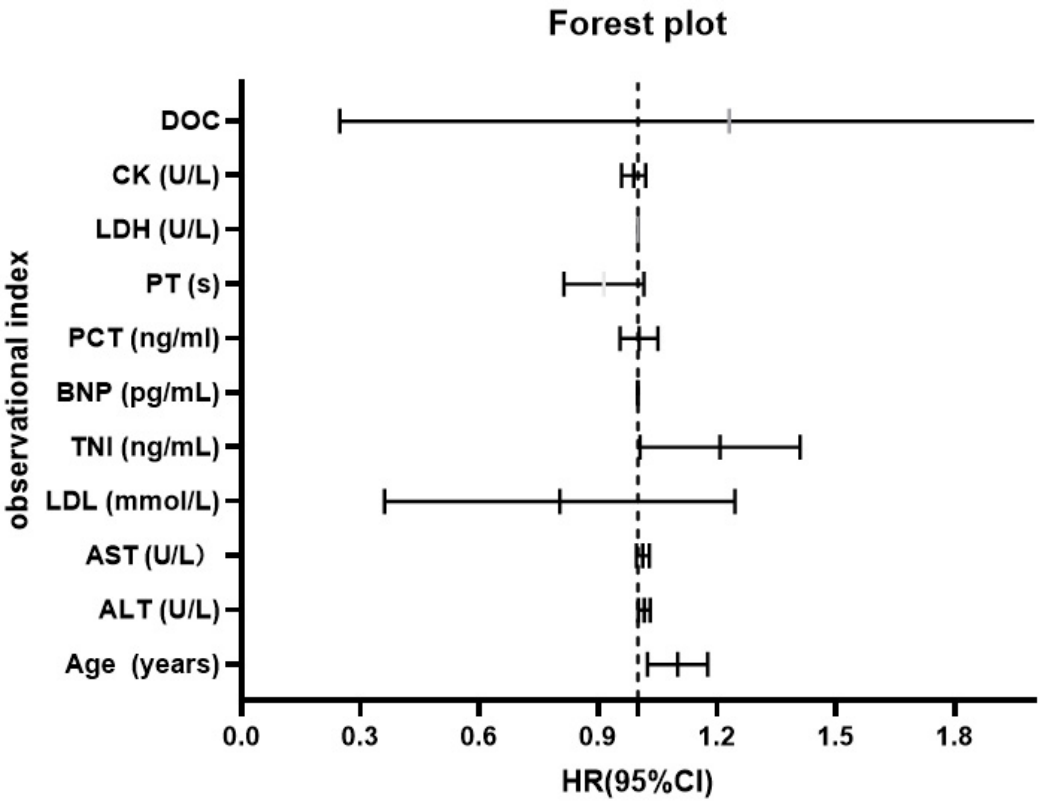

Fig. 1. Forest plot of multivariate COX regression analysis. ALT, Alanine transaminase; AST, Aspartate transaminase; LDL, low-density lipoprotein; TNI, Troponin I; BNP, brain natriuretic peptide; PCT, procalcitonin; PT, prothrombin time; LDH, lactate dehydrogenase; CK, creatine kinase; DOC, disturbance of consciousness; HR, hazard ratio.

Table 5. ROC curve analysis of sHLH.

Observation index	AUC	Youden's index	*p*-value	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)
Age (years)	0.891	0.685	<0.001	0.817–0.965	63.5	82.8	85.7
ALT (U/L)	0.617	0.229	0.077	0.489–0.745	41	58.6	64.3
AST (U/L)	0.834	0.649	<0.001	0.732–0.945	111	82.8	82.1
TNI (ng/mL)	0.882	0.621	<0.001	0.808–0.957	2.15	62.1	100

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristics; sHLH, secondary hemophagocytic lymphohistiocytosis; ALT, Alanine transaminase; AST, Aspartate transaminase; TNI, Troponin I.

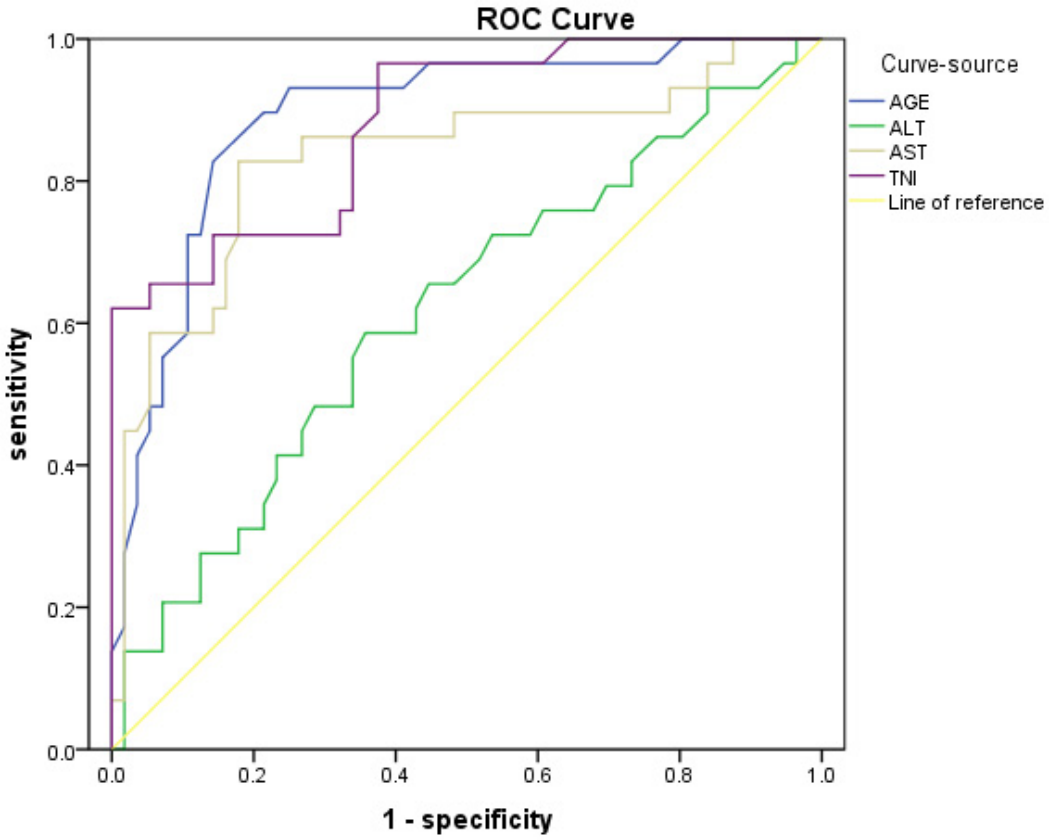

Fig. 2. ROC curve of sHLH. 1-Specificity is determined by measuring the abscissa indicating false positive rate, and sensitivity is determined by measuring the ordinate indicating true positive rate. The four variables analyzed were age (blue line, years), Alanine transaminase (ALT; green line, U/L), Aspartate transaminase (AST; yellow line, U/L), and Troponin I (TNI; purple line, ng/mL).

egy involved a combination of antibiotics with steroids and gamma globulin. The findings from two well-known clinical studies, HLH94 and HLH-2004, along with other observational studies, indicate that allogeneic hematopoietic stem cell transplantation is the only effective means to mitigate the effects of primary diseases in various types of HLH, thereby improving the long-term survival rates (Ramos-Casals et al, 2014; Yoon et al, 2020). However, large-scale clinical studies have also revealed that two-thirds of the mortality rates occur before patients receive al-

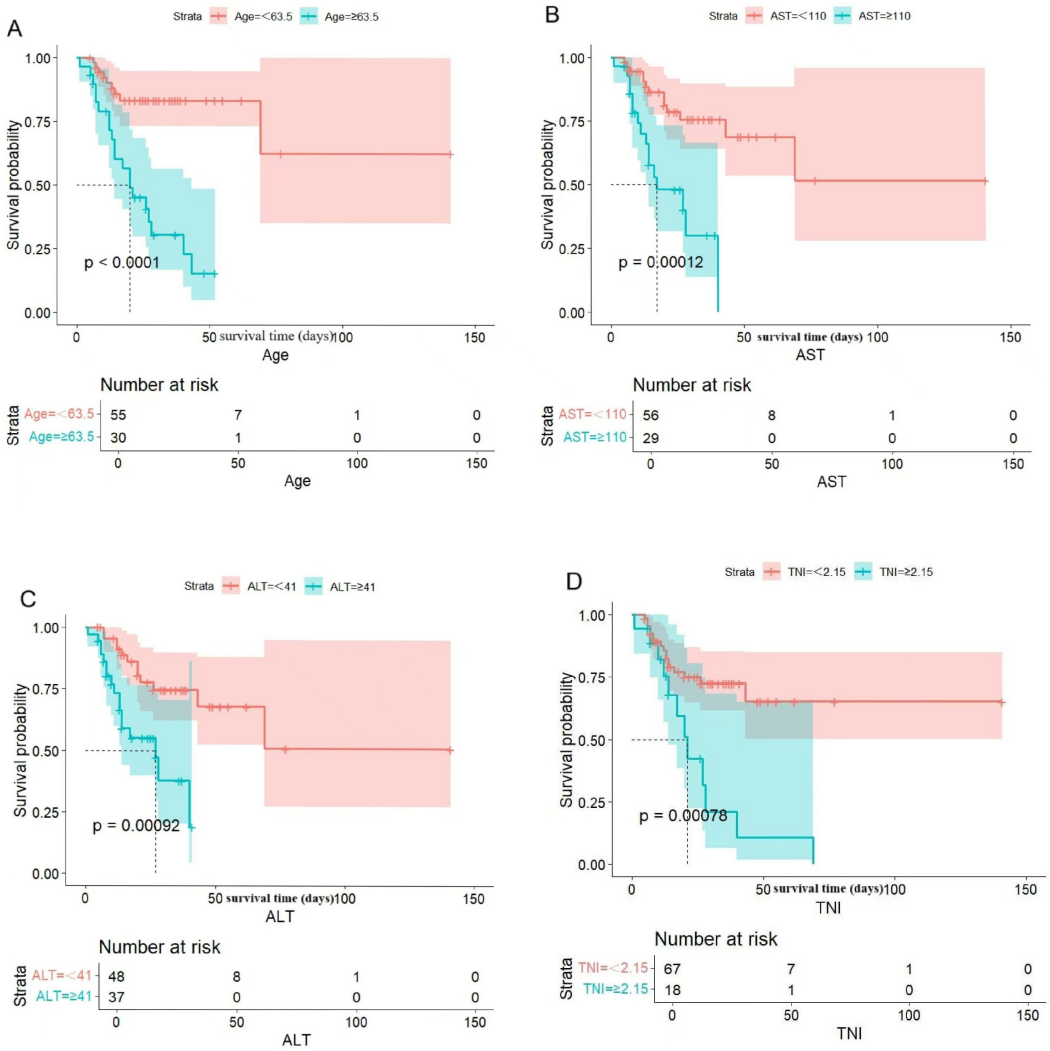

Fig. 3. Kaplan-Meier survival analysis and the risk table of independent risk factors for sHLH. (A) Age (years). (B) Aspartate transaminase (AST; U/L). (C) Alanine transaminase (ALT; U/L). (D) Troponin I (TNI; ng/mL). The vertical axis denotes the survival probability while the horizontal axis denotes the survival time (days).

logeneic hematopoietic stem cell transplantation, predominantly within the first 8 weeks of induction treatment. This highlights the high risk of early death among sHLH patients (Bhatt et al, 2019; Paul et al, 2022; Ramos-Casals et al, 2014; Wei et al, 2021; Yoon et al, 2020; Zhou et al, 2020).

Timely identification of high-risk patients and individualized treatment approaches are crucial for reducing mortality rates (Bhatt et al, 2019; Paul et al, 2022; Ramos-Casals et al, 2014; Wei et al, 2021). Consequently, this study primarily investigates the high-risk factors associated with mortality in HLH patients, which can aid in rapid identification of HLH patients in the early stages of the disease and provide a theoretical basis for treatment.

Our findings indicate that patients aged ≥63.5 years, with AST levels ≥111 U/L, ALT ≥41 U/L and TNI levels ≥2.15 ng/mL, are independent risk factors for mortality, which can be translated into a higher risk of death and poorer prognosis. We performed a relevant literature review to gain a sense of the potential pathophys-

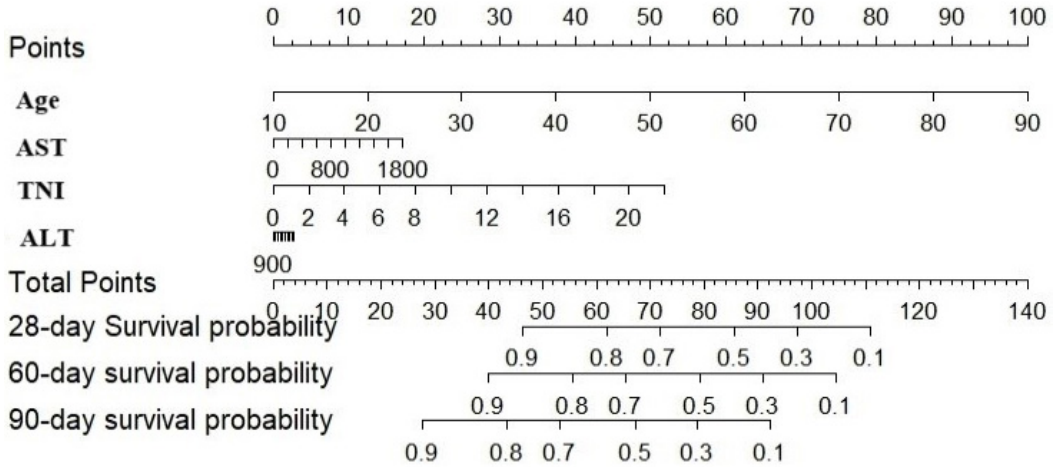

Fig. 4. Nomogram prediction model of mortality risk. The corresponding line segments of each variable are marked with scales, representing the value range of the variable, and the length of the line segment reflects the contribution of the factor to the outcome event. The score includes the single item score, namely the point, which represents the corresponding single item score of each variable at different values, and the total score, namely the total points, which represents the total score of the corresponding single item score after the values of all variables are added up. Survival probabilities were predicted at 28, 60, and 90 days, respectively. ALT, Alanine transaminase; AST, Aspartate transaminase; TNI, Troponin I.

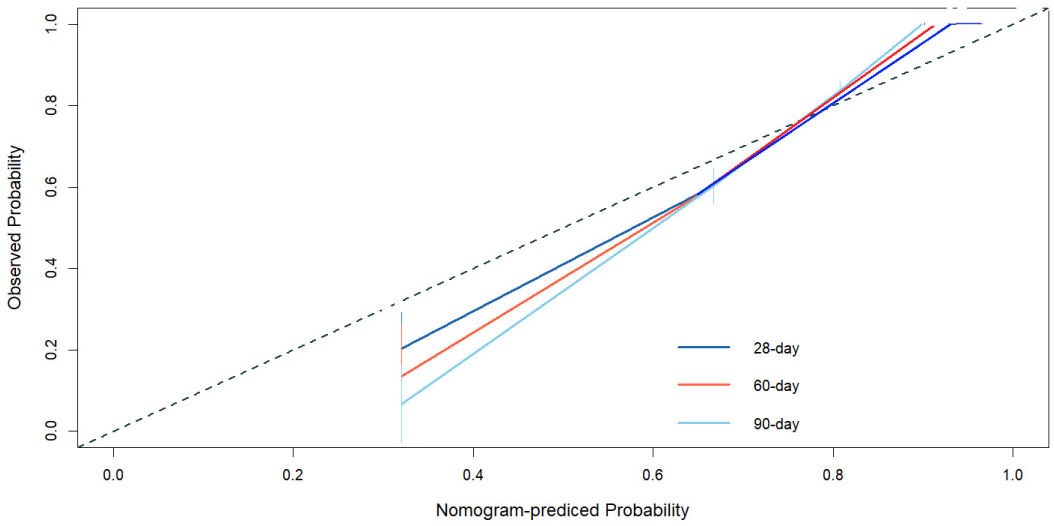

Fig. 5. Calibration curves of survival rates of sHLH patients at 28, 60 and 90 days. Predicted event rate risk is determined by measuring the abscissa, and observed event rate risk, which can be interpreted as the event rate (percentage), is determined by measuring ordinate ranging from 0 to 1. The dashed line on the diagonal is the reference line, which is the case where the predicted value = the actual value. The red line is the curve fitting line, and the blue error bars represent the 95% CIs.

iological mechanisms, which involve the independent risk factors identified in this study, behind the increased risk of death in sHLH patients. The pathology of sHLH lies in an overwhelming cytokine storm triggered by various etiologies. When the cytokine storm becomes uncontrollable, it can lead to catastrophic consequences such as multi-organ failure. Relevant literature indicates that elderly patients have

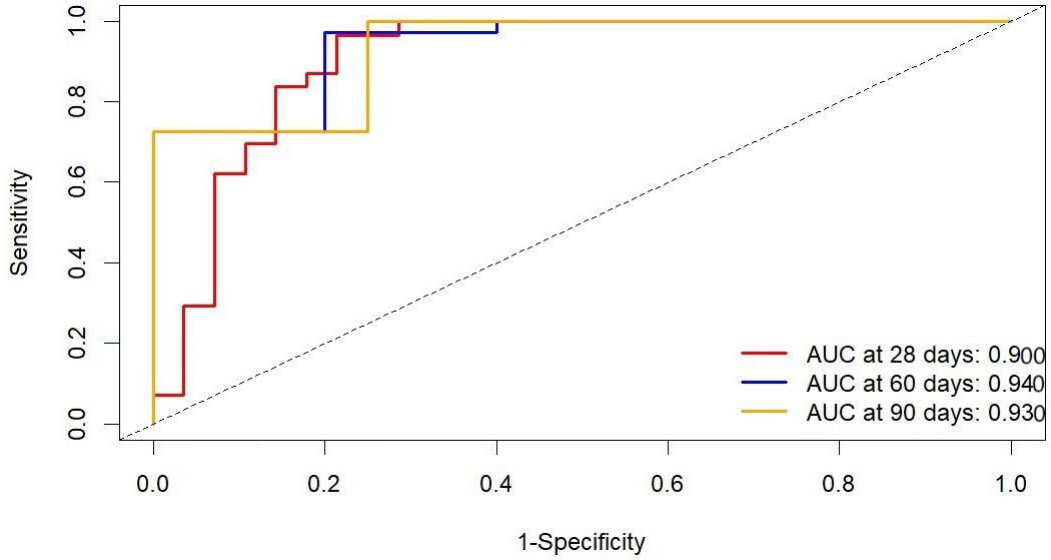

Fig. 6. ROC curves of the prediction model for mortality risk at 28, 60 and 90 days in sHLH patients. AUC, area under the curve; ROC, receiver operating characteristics; sHLH, secondary hemophagocytic lymphohistiocytosis.

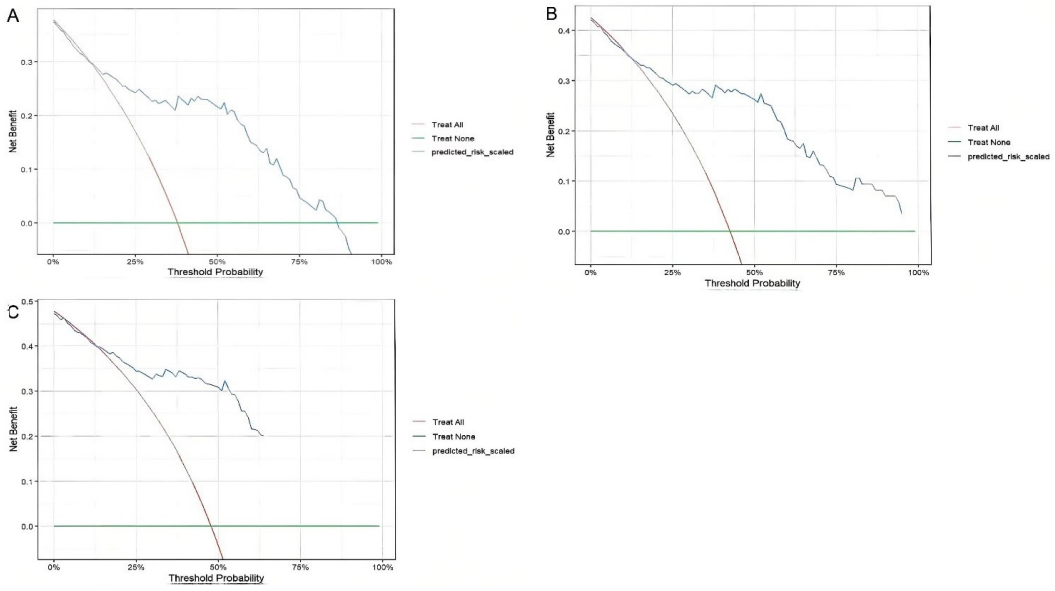

Fig. 7. Decision curve analysis (DCA) of sHLH patients at 28 (A), 60 (B) and 90 days (C). The red line represents the "treat all" model, and the green line represents the "treat none" model. The blue line is the DCA model, the abscissa represents the threshold probability, and the ordinate represents the net benefit.

lower resistance to inflammatory storms, are less responsive to or even intolerant to drug treatment, and suffer more complications (Deng et al, 2023; Zhang et al, 2022). The elevated levels of ALT and AST imply the occurrence of acute liver injury in patients with sHLH. It has been shown that sHLH-related acute liver injury in 24.5% of patients may progress to acute liver failure, and then hepatomegaly, coagulation dysfunction and other conditions, eventually leading to death (Böhm et al, 2024; Lu et al, 2021; Orth et al, 2024). The increased TNI level provides indi-

cations of myocardial damage, even myocardial necrosis, and cardiac dysfunction due to the inflammatory cell storm, which justify the high fatality rate of this disorder (Deng et al, 2023; Meng et al, 2021; Orth et al, 2024). Therefore, we established a predictive model for the mortality risk in sHLH. Using the nomogram, clinicians can estimate the 28-, 60-, and 90-day survival rates of patients after disease onset, facilitating a more intuitive calculation of survival probabilities. The reliability of the model was validated through the calculation of the C-index, calibration curves, and clinical decision curves.

In a study by Zhu et al (2023), a multivariate regression analysis of 126 patients with sHLH showed that lymphocyte count $<0.45 \times 10^9$/L, APTT $\geq$39.7 s, and ALB $<$25.9 g/L were independent risk factors for death within 30 days. Zhang et al (2023) reported that independent risk factors for early mortality in newly diagnosed sHLH patients included age $>$60 years, platelet count $\leq 20.0 \times 10^9$/L, APTT $>$36.0 s, and LDH $>$1000.0 U/L ($p < 0.05$). Similarly, Lu et al (2021) identified four independent factors for poor prognosis: male gender, alterations in mental state, serum ferritin levels $\geq$31,381 µg/L, and IL-6 levels $\geq$18.59 pg/mL. Patients exhibiting changes in mental state, elevated serum ferritin, and increased IL-6 levels were found to have a higher risk of mortality. Nevertheless, these studies are primarily limited by low C-index and poor reliability of their models. Additionally, these clinical studies were primarily conducted by haematologists, who are not typically the first clinicians involved in diagnosing and treating patients with hemophagocytic syndrome, recruiting and selecting study subjects who had already passed the point entailing highest risk of death. In contrast, our study specifically examines patients with HLH who were initially diagnosed in the emergency department, thereby providing a more accurate predictive value for early mortality risk.

The present study has some limitations, such as insufficient sample size and the adoption of retrospective design in studying the existing clinical databases, with the latter posing limitations resulting in inevitable data gaps in most cases as these databases are not specifically designed for clinical research. Furthermore, the absence of certain collected variables may hinder the assessment of potential influences on outcomes. While the common practice in retrospective studies is to solicit details from patients through recalling, this approach might introduce "recall bias". Besides, the generalizability of the present set results to other populations is not recommended due to the single-centre study design. This study also lacked external validation of the model, and the treatments offered to the patients in this study may not be as professional as those given by the haematologists. We hypothesize that the discrepancies in findings between our study and others in literature may be attributed to the single-center retrospective nature of these studies and variations in sample sizes. To address this, we plan to gradually increase our sample size and conduct multi-centre prospective studies to further validate the accuracy of our prediction model, with a goal to improve and optimize it.

Regarding treatment, sHLH patients admitted to the emergency department of our institution primarily receive corticosteroids and gamma globulin. In contrast, the use of rituximab and etoposide is less common. Most patients in the haematol-

ogy department are treated with etoposide as a first-line therapy prior to transplantation. Böhm et al (2024) found that the survival rates of patients receiving first-line etoposide treatment improved both before and after hematopoietic stem cell transplantation, with rates of 83%–91% and 70%–88%, respectively. These findings may serve as a benchmark for developing new treatment regimens. In view of this, our future investigations will consider extending the analysis to treatment responses among hospitalized patients both before and after transplantation.

Conclusion

In conclusion, patients with sHLH have atypical clinical features and high early mortality. sHLH patients with age ≥63.5 years, ALT level ≥41 U/L, AST level ≥111 U/L and TNI level ≥2.15 ng/mL are associated with higher risk of death. Our risk prediction model established based on the results of COX regression analysis can aid in early identification of sHLH patients with high risk of death.

Key Points

- sHLH is a rapidly progressive and highly lethal rare disease. Patients often survive for less than 2 months without any therapeutic intervention. Timely identification of high-risk sHLH patients is particularly important for clinicians.
- Univariate and multivariate COX regression analyses were performed to develop a mortality risk prediction model, revealing that the age, Alanine transaminase (ALT), Aspartate transaminase (AST) and Troponin I (TNI) were significant independent risk factors affecting the prognosis of patients with sHLH.
- The receiver operating characteristic (ROC) curve analysis revealed that age ≥63.5 years, ALT levels ≥41 U/L, AST levels ≥111 U/L and TNI levels ≥2.15 ng/mL are independent risk factors for death in patients with hemophagocytic syndrome.
- The mortality risk prediction model developed in this work showed superior accuracy in predicting the survival rate of patients at 28, 60, and 90 days.

Availability of Data and Materials

The data analyzed was available on the request for the corresponding authors.

Author Contributions

KW, WCW and JHZ designed the study. KW, WCW collected the data. KW and MH performed the experiments. KW and WCW analyzed the data. KW, JHZ and WCW drafted the manuscript. All authors contributed to the important editorial

changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This research received approval from the Ethics Committee of Peking University People's Hospital (No. 2024PHB066-001), and informed consent to participate was obtained from patients or their relatives. This study was conducted in adherence with the guidelines outlined in the Declaration of Helsinki.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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