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Machine learning-based prognostic model for bloodstream infections in hematological malignancies using Th1/Th2 cytokines

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Abstract

Objective Bloodstream infection (BSI) is a significant cause of mortality in patients with hematologic malignancies(HMs), particularly amid rising antibiotic resistance. This study aimed to analyze pathogen distribution, drug-resistance patterns and develop a novel predictive model for 30-day mortality in HM patients with BSIs.

Methods A retrospective analysis of 231 HM patients with positive blood cultures was conducted. Logistic regression identified risk factors for 30-day mortality. Th1/Th2 cytokines were collected at BSI onset, with LASSO regression and restricted cubic spline analysis used to refine predictors. Seven machine learning(ML) algorithm (XGBoost, Logistic Regression, LightGBM, RandomForest, AdaBoost, GBDT and GNB) were trained using 10-fold cross-validation and model performance was evaluated with the ROC, calibration plots, decision and learning curves and the Shapley Additive Explanations (SHAP) analysis. The predictive model was developed by integrating Th1/Th2 cytokines with clinical features, aiming to enhance the accuracy of 30-day mortality prediction.

Results Among the cohort, acute myeloid leukemia (38%) was the most common HM, while gram negative bacteria (64%) were the predominant pathogens causing BSI. Age, polymicrobial BSI, IL-4, IL-6 and AST levels were significant predictors of 30-day mortality. The Logistic Regression model achieved AUCs of 0.802, 0.792, and 0.822 in training, validation, and test cohorts, respectively, with strong calibration and clinical benefit shown in decision curves. SHAP analysis highlighted IL-4 and IL-6 as key predictors.

Conclusions This study introduces a novel ML-based model integrating Th1/Th2 cytokines and clinical features to predict 30-day mortality in HM patients with BSIs, demonstrating strong performance and clinical applicability.

Keywords Bloodstream infection, Hematological malignancy, Machine learning, Model, Microbiology, Resistance, Risk factor

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Introduction

Bloodstream infection (BSI) is a common and severe clinical condition caused by the invasion and proliferation of various pathogens in the bloodstream. These microorganisms release toxins and metabolic products, inducing cytokine release and triggering systemic inflammatory responses that can progress to multi-organ dysfunction syndrome or death in severe cases [1]. Advances in chemotherapy, targeted therapies, hematopoietic stem cell transplantation, and supportive care have significantly improved the prognosis of patients with hematologic malignancies(HMs). However, due to the underlying characteristics of HMs, chemotherapy-induced neutropenia, and immunosuppression from treatments, the immune system is often compromised, leading to an increased susceptibility to BSIs, with an incidence reported at 20.8-24.1% [2–8]. In addition, patients with HMs are particularly prone to polymicrobial or recurrent BSIs. BSIs in these patients can exacerbate their condition, disrupt or delay chemotherapy, and significantly increase mortality [5, 9].

BSI is a major challenge in the treatment of patients with HMs, particularly in the context of increasing antibiotic resistance. Early identification and effective control of BSIs are crucial for improving the prognosis and survival of patients. In addition to studying pathogen distribution patterns and antibiotic resistance to guide clinicians in choosing appropriate antibiotics, identifying risk factors that affect the prognosis of BSI patients and developing predictive models can aid in early intervention and optimize patient management, ultimately reducing mortality and improving outcomes. Current research has identified several risk factors for poor BSI prognosis in HM patients, including age > 60 years, relapsed or refractory malignancies, nosocomial infections, prolonged or severe neutropenia, inappropriate empirical antibiotic therapy, albumin < 30 g/L, septic shock, multidrug-resistant (MDR) bacteria, central venous catheter placement, urinary catheterization, and thrombocytopenia [4, 7, 10–12]. However, predictive models based on these clinical features often yield suboptimal results and require further validation.

Cytokines are powerful weapons used by immune cells to combat infections. Th1 cytokines, including interleukin-2 (IL-2), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), and Th2 cytokines, including interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-10 (IL-10), are involved in mediating cellular immunity and humoral immune responses, respectively. Th1/Th2 cytokines are typically balanced, but this equilibrium can be disrupted by tumors, inflammation, or infections. Studies have shown that increased Th1/Th2 cytokines can provide diagnostic value for infections [13–20]. However, research on the relationship between Th1/Th2 cytokine levels during infection and BSI prognosis in patients with HMs is limited. This gap highlights the need for innovative approaches that combine Th1/Th2 data with clinical features to enhance mortality risk prediction models.

Machine learning (ML), as an emerging technology in medicine, can efficiently handle complex biomedical data and has shown significant advantages in building predictive models. In recent years, ML has made remarkable strides in the field of medicine, revolutionizing disease diagnosis, prognosis prediction, and clinical decision-making. Its applications span various medical domains, including oncology, cardiology, infectious diseases, and personalized medicine. By leveraging large-scale patient data, ML algorithms can enhance diagnostic accuracy, identify disease patterns, predict patient outcomes, and optimize treatment strategies. These innovations not only improve healthcare efficiency but also contribute to more precise and individualized patient care [21–25], helping clinicians identify high-risk patients early, enabling timely intervention and treatment [26, 27], ultimately leading to better clinical outcomes. This study focuses on identifying risk factors for 30-day mortality in BSI patients with HMs, constructing predictive models using ML classification methods, and evaluating Th1/Th2 cytokines as potential biomarkers. By integrating these risk factors, we aim to develop an improved 30-day mortality prediction model for BSI through ML, promoting personalized interventions and enhancing patient management precision.

Materials and methods

Source of data

This was a real-word single-center cohort study conducted at the Department of Hematology, Affiliated Hospital of Southwest Medical University. The study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University. The study was retrospectively designed, and the requirement for informed consent was therefore waived. Data of 249 patients with positive blood cultures (bacteria or fungi) in HMs hospitalized from 1 January 2019 to 31 December 2023 were collected from the electronic medical record.

Study patients

Inclusion criteria were as follows: (1) patient diagnosed with HM; (2) positive blood culture; (3) complete clinical data. Exclusion criteria were: (1) patient diagnosed with non-HM; (2) incomplete clinical data; (3) patient with multiple positive blood cultures with the same pathogen during the same hospital stay; they were counted once; (4) patients with Hemophagocytic Syndrome (HLH).

Definitions

Patients with positive blood culture (excluding pollution) who had a fever (> 38 °C) and at least one of the following symptoms: chills, low oxygen saturation, hypotension, cold moist limbs, or altered consciousness, were identified as true BSI [28]. Polymicrobial bloodstream infection (Polymicrobial BSI) were defined as cases in which two or more distinct pathogens were simultaneously cultured from the venous blood samples based on the above-mentioned symptoms. MDR bacteria were defined as resistant to three or more antibacterial agents [29]. For common skin contaminants such as *Diphtheroids*, *Bacillus spp*, *Propionibacterium spp*, *coagulase-negative staphylococci* (CoNS), *Viridans Streptococci*, *Aerococcus spp*, and *Micrococcus spp* [30, 31], detection in 2 or more separate blood cultures was required for a definite BSI diagnosis. Repeated sampling from the same patient at the same site was also excluded. Pulmonary infection was diagnosed in patients with acute respiratory symptoms and new onset of pulmonary infiltration on chest computed tomography. Gastrointestinal symptoms included abdominal pain, diarrhea, or lower gastrointestinal bleeding. Perianal infections were defined by perianal pain, abscess, fistula, gangrene or scrotal infection. Absolute neutrophil counts $< 0.5 \times 10^9$/l were defined as neutropenia.

Study Predictors

Based on previous literature and the expertise of hematology physicians regarding 30-day mortality risk factors post-BSI, relevant factors were collected. While predictive factors with data loss exceeding 30% were excluded (e.g., D dimer and FDP). Clinical variables recorded for risk factor analysis and model development included age, gender, history of hypertension, history of diabetes, pathogens of BSIs, results of drug sensitivity test, state of disease, nosocomial infection, concurrent infection, white blood cell count, neutrophil count, platelet count, albumin level, procalcitonin (PCT), Creatinine (Crea), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), serum albumin (ALB), Total bilirubin (TB), Direct bilirubin (DB), Indirect bilirubin (IB), Th1/Th2 cytokines and outcomes at 30-day after BSI.

Detection of Th1/Th2 cytokines

Two milliliters of blood were collected in serum separator tubes. After clotting at room temperature or centrifugation at 2000–4000 rpm for 20 min, approximately 0.5 mL of serum was separated and sent for analysis. All samples were processed within 4 h of collection. Cytokine levels, including IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α (pg/mL), were measured using a CytoFLEX flow cytometer.

Model development and evaluation

In order to improve the accuracy and statistical power of the estimators, we conducted univariate and multivariate logistic regression analysis on all patients with complete clinical indicators to screen for 30-day mortality risk factors. Variables with $p < 0.05$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. Final independent clinical risk factors were determined through logistic multivariate regression with $P < 0.05$. The Least Absolute Shrinkage and Selection Operator (LASSO) method was employed to select parameters with non-zero coefficients.

After selecting characteristic factors from all independent variables, we divided HM patients into training set and test set. Subsequently, seven ML models, including Extreme Gradient Boosting (XGBoost), Logistic Regression (LR), Light Gradient Boosting Machine (LightGBM), RandomForest (RF), Adaptive Boosting (AdaBoost), Gradient Boosting Decision Tree (GBDT) and Gaussian Naïve Bayes (GNB) were developed and refined by applying a 10-fold cross-validation methodology. The performance of these models was assessed using various metrics, including the area under the receiver operating characteristic curve (ROC), calibration, decision and learning curves and confusion matrix. Finally, the SHAP (Shapley Additive Explanations) method was applied to interpret the predicted outcomes and clarify the influence of each feature on the model's predictions. This approach provides valuable insights, offering clinicians a practical reference for informed decision-making.

Statistical analysis

The continuous variables were expressed as mean ± standard deviation or median (IQR) and compared using t-test or Mann-Whitney U test, while categorical variables were expressed in number and percentage and compared using Chi-square test and Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for 30-day mortality risk factors analysis using the logistic regression. Variables with $p < 0.05$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The cut-off value for Th1/Th2 cytokines was determined through restricted cubic spline (RCS) regression. Non-linear continuous variables were categorized based on the cut-off values during model construction. All Statistical analyses were performed using R version 4.2.3 and python version 3.11.4.

Results

Patient characteristics

A total of 249 patients with positive blood cultures in HMs were screened, and 231 were finally included in the study based on the exclusion criteria. The overall

workflow of the study is shown in Fig. 1. The cohort consisted of 88 patients with acute myeloid leukemia (AML), 53 with acute lymphocytic leukemia (ALL), 25 with lymphoma, 20 with Myelodysplastic syndromes (MDS), 12 with Multiple Myeloma (MM) and 33 with other HMs (Table 1). Table 1 presents the baseline clinical characteristics of HM patients with BSI, divided into survival and death groups. The 30-day mortality in patients with HMs after BSIs was 25.54%. The median age of the patients was 50 years (range 39–61), with 123 (53%) being male, and 108 (47%) being female. The state of 49 patients with HMs was relapsed/refractory. A majority (78%) had concurrent pulmonary infections. Neutropenia existed in 73% of patients. BSIs with MDR bacteria occurred in 105 patients.

Microbiology

Two hundred fifty-one pathogens were isolated from blood culture, including gram-negative bacteria (63.64%), gram-positive bacteria (22.51%), fungi (5.63%) and polymicrobial BSI (8.23%) (Fig. 2). The most common gram-negative bacterium was *Escherichia coli*, accounting for 29.08%, followed by *Klebsiella pneumoniae* (21.12%) and *Pseudomonas aeruginosa* (7.57%). 20 strains of *carbapenem resisant enterbacteriaceae* (CRE) were detected in *Klebsiella pneumoniae* and *Escherichia coli*. The common gram-positive bacteria were CoNS (7.17%), *Staphylococcus aureus* (7.17%), and *Enterococcus faecium* (5.18%). Six strains of *methicillin-resistant Staphylococcus aureus* (MRSA) and sixteen strains of *methicillin-resistant coagulase-negative staphylococcus* (MRCNS) were detected in all of *Staphylococcus aureus* and CoNS. The most common fungus was *Candida tropicalis*, accounting for about 5.6%. Among the 19 cases of Polymicrobial BSI, 18

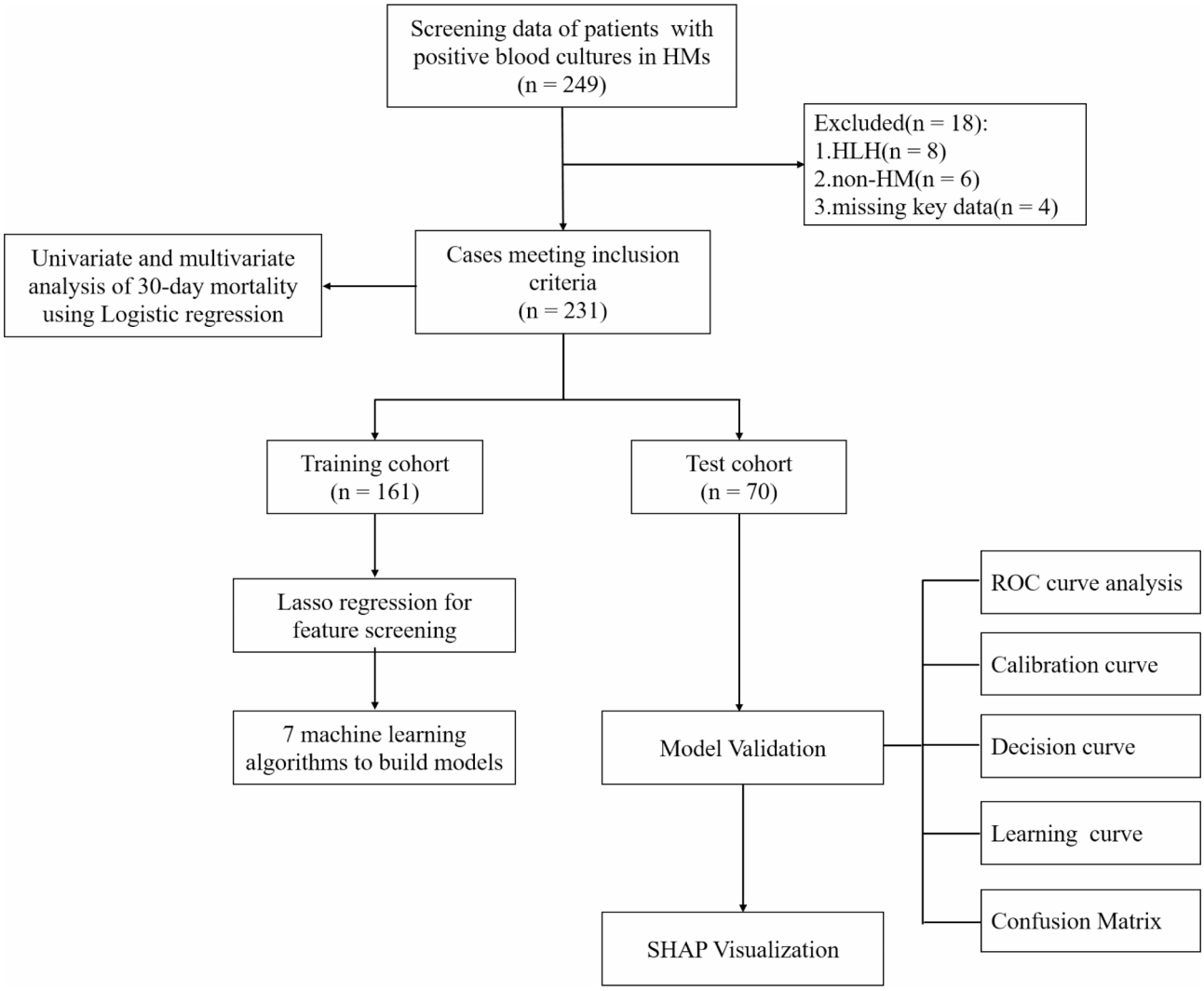

Fig. 1 Participant flow diagram

Table 1 Characteristics of all patients ($n=231$)

Variable	Overall, $N=231$[1]	Survivors, $N=172$[1]	Death, $N=59$[1]	*P*-value[2]
Gender, n (%)				0.90
Male	123 (53)	92 (53)	31 (53)	
Female	108 (47)	80 (47)	28 (47)	
Age, Median (IQR)	50.00 (39.00–61.00)	50.00 (39.50–59.00)	51.00 (39.00–68.00)	0.22
Relapsed/refractory HMs, n (%)	49 (21)	31 (18)	18 (31)	0.043
Neutropenia, n (%)	168 (73)	123 (72)	45 (76)	0.48
Basic disease, n (%)	66 (29)	47 (27)	19 (32)	0.47
Diagnosis, n (%)				0.011
AML	88 (38)	64 (37)	24 (41)	
ALL	53 (23)	45 (26)	8 (14)	
Lymphoma	25 (11)	22 (13)	3 (5.1)	
MDS	20 (8.7)	14 (8.1)	6 (10)	
MM	12 (5.2)	10 (5.8)	2 (3.4)	
Other	33(14.5)	17(9.9)	16(26.8)	
Disease status, n (%)				< 0.001
Initial consultation	91 (39)	63 (37)	28 (47)	
CR/PR	79 (34)	73 (42)	6 (10)	
NR/relapse/PD	61 (26)	36 (21)	25 (42)	
Pathogens, n (%)				< 0.001
Gram-negative bacteria	147 (64)	115 (67)	32 (54)	
Gram-positive bacteria	52 (23)	45 (26)	7 (12)	
Fungi	13 (5.6)	7 (4.1)	6 (10)	
Polymicrobial BSI	19 (8.2)	5 (2.9)	14 (24)	
MDR, n (%)	105(47.297)	80(47.337)	25(47.170)	0.983
Concurrent pulmonary infection, n (%)	180 (78)	133 (77)	47 (80)	0.71
Concurrent perianal infection, n (%)	20 (8.7)	14 (8.1)	6 (10)	0.63
Concurrent intestinal infection, n (%)	18 (7.8)	13 (7.6)	5 (8.5)	0.78
PLT, Median (IQR)	13.00 (4.00–36.00)	17.50 (4.00–41.50)	9.00 (3.00–21.00)	0.022
ALB, Median (IQR)	31.90 (28.60–36.30)	32.50 (28.95–37.25)	30.30 (25.40–34.70)	0.003
ALT, Median (IQR)	22.20 (12.70–50.00)	21.50 (13.10–44.70)	31.40 (12.40–103.40)	0.032
AST, Median (IQR)	22.30 (12.70–40.60)	21.35 (11.95–32.80)	38.70 (14.40–108.80)	< 0.001
TB, Median (IQR)	15.80 (10.30–24.00)	14.85 (9.55–21.20)	17.80 (11.30–37.50)	0.005
DB, Median (IQR)	7.00 (4.10–11.80)	5.80 (3.55–10.05)	10.90 (5.90–22.40)	< 0.001
PCT, Median (IQR)	1.57 (0.36–11.42)	1.19 (0.31–9.62)	3.07 (1.15–19.25)	0.004
IL-2, Median (IQR)	3.00 (1.66–5.35)	3.05 (1.58–5.79)	2.97 (2.01–4.66)	0.82
IL-4, Median (IQR)	2.49 (1.29–3.49)	2.23 (1.22–3.11)	3.16 (1.98–3.89)	0.004
IL-6, Median (IQR)	875.00 (165.71–3,799.88)	610.12 (146.37–2,304.15)	2,241.75 (431.40–6,184.47)	< 0.001
IL-10, Median (IQR)	107.46 (21.06–480.16)	72.75 (18.70–381.45)	344.18 (35.56–967.48)	< 0.001
TNF-α, Median (IQR)	4.59 (2.78–7.37)	4.13 (2.58–6.31)	6.37 (4.15–18.04)	< 0.001
IFN-γ, Median (IQR)	7.29 (3.14–15.84)	6.69 (2.97–13.90)	8.46 (3.96–55.05)	0.022

[1]Median (IQR) or Frequency (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

involved two pathogens and one involved three, with 11 cases were *Escherichia coli* combined with gram-negative bacteria, gram-positive bacteria, or fungi (Fig. 2).

The results of the drug sensitivity test for the common pathogens are exhibited in Fig. 3. *Escherichia coli* had the lowest rate of antibiotic resistance to tigecyoline (2.74%), followed by amikacin (4.11%), meropenem (10.96%) and imipenem (10.96%). The rates of antibiotic resistance of *Klebsiella pneumoniae* to tigecyoline, amikacin, imipenem, and meropenem were 3.77%, 5.66%, 24.53%, and 24.53%, respectively. The frequencies for ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* strains were 43.84% and 22.64%, respectively. *Pseudomonas aeruginosa* had the lowest rates of antibiotic resistance to amikacin, levofloxacin and cefoperazone sulbactam, which were 0%, 0%, 5.26%, respectively. MRSA had no antibiotic resistance to linezolid and vancomycin. MRCNS was completely sensitive to linezolid and vancomycin. *Enterococcus faecium* had no resistance to vancomycin and linezolid. Fungal resistance was relatively high to voricozole

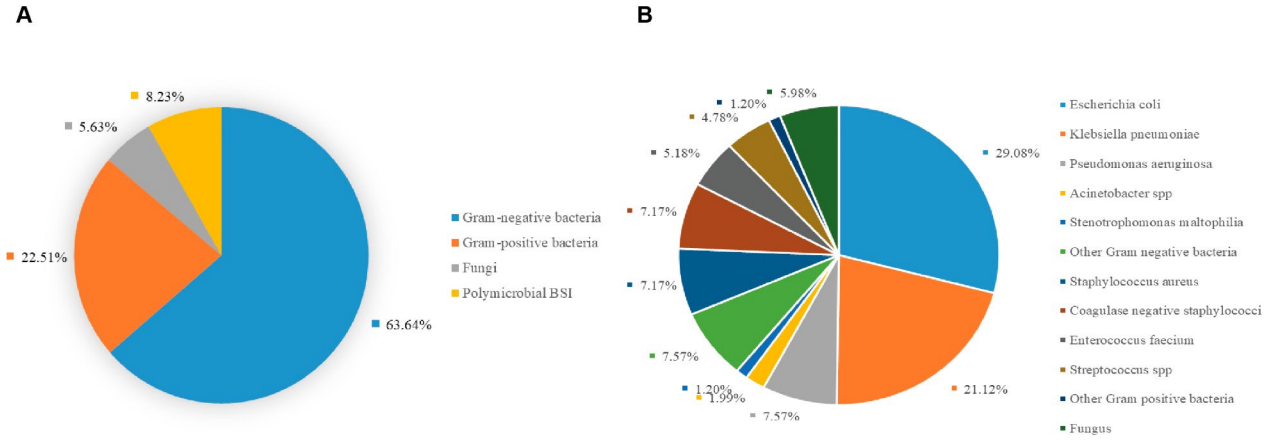

Fig. 2 Microbiological results of BSIs among patients with HMs. (**A**) Distribution of pathogens causing BSIs in patients with HMs. (**B**) Proportion of different pathogens responsible for BSIs in this patient cohort

(53.85%) and flucozole (46.15%). Meanwhile, no fungus resistant to amphotericin B, caspofungin and micafungin was found in this study.

Th1/Th2 cytokines

We performed a correlation analysis on the six Th1/Th2 cytokines (IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α) based on the normality of the data distribution. The results revealed a positive correlation between IL-6 and IL-10 ($r = 0.74$), IL-6 and TNF-α ($r = 0.55$), and IL-2 and IL-4 ($r = 0.5$), as shown in Supplementary Fig. 1. In addition, in 231 patients, we utilized RCS to ascertain the cut-off values for IL-4, IL-6, IL-10, IFN-γ and TNF-α levels. The distribution of IL-4, IL-10, TNF-α and IFN-γ was found to be non-linear. The risk of 30-day mortality increased when IL-4 levels exceeded 2.492 pg/mL, IFN-γ levels surpassed 7.29 pg/mL, TNF-α exceeded 4.59 pg/mL, and IL-10 levels were higher than 107.46 pg/mL. Conversely, the distribution of IL-6 exhibited linearity, with a heightened risk of mortality when levels exceeded 875 pg/mL (Supplementary Fig. 1).

Clinical risk factors of 30-day mortality

To enhance the accuracy and statistical power of the estimators, univariate and multivariate logistic regression analyses were performed on all patients with complete clinical data to screen the risk factors for 30-day mortality. Univariate logistic regression analysis revealed that factors such as age > 60 years, relapsed/refractory HM, disease status, polymicrobial BSI, IL-4 > 2.492 pg/mL, IL-10 > 107.46 pg/mL, TNF-α > 4.59 pg/mL, IL-6 levels, ALB < 30 g/L, PLT, ALT, AST, TB, and DB were significantly associated with 30-day mortality following BSI ($p < 0.05$ for all, Table 2). Further multivariate logistic regression analysis identified the following independent prognostic factors for 30-day mortality after BSI in patients with HMs: age > 60 years ($p = 0.023$, OR = 2.79, 95% CI: 1.15–6.77), disease status ($p = 0.004$, OR = 0.17, 95% CI: 0.05–0.58), polymicrobial BSI ($p < 0.001$, OR = 14.02, 95% CI: 3.55–55.48), IL-4 > 2.492 pg/mL ($p = 0.008$, OR = 3.21, 95% CI: 1.36–7.57), IL-6 ($p = 0.021$, OR = 1.00, 95% CI: 1.00–1.00), and AST ($p = 0.003$, OR = 1.01, 95% CI: 1.00-1.02) (Table 2).

Predictors selection

A total of 231 patients with positive blood cultures in HMs were divided into a training group (161 patients) and a test group (70 patients) following a 7:3 ratio, after addressing data imbalance. Statistical analysis revealed no significant differences between the two groups except for the gender ($p = 0.005$) and TB ($p = 0.007$) (Table 3). LASSO regression is a regularization technique that performs variable selection and adjusts model complexity by incorporating penalty terms into an optimization objective. In this study, LASSO coefficient curves were generated for five non-zero variables (age, polymicrobial BSI, IL-4 levels, IL-6 levels, and AST) at the Lambda.1se value of 0.057, using 10-fold cross-validation (Fig. 4).

Comprehensive analysis of classified multi-model

XGBoost, LR, LightGBM, RandomForest, AdaBoost, GBDT, and GNB were trained and evaluated through 10 repetitions. Model performance was assessed using the area under the curve (AUC). The results showed that XGBoost, RandomForest, GBDT, LightGBM, AdaBoost, and LR performed the best in the training set, while Logistic Regression achieved the highest AUC in the validation set (Fig. 5A-B, Supplementary Tables 1-–2). To further assess the clinical applicability and compare the performance of the seven models, decision curve analysis (DCA) and calibration curves were analyzed. The DCA demonstrated that the LR model provided better clinical utility, suggesting its superior suitability for clinical decision-making (Fig. 5C). The calibration curves

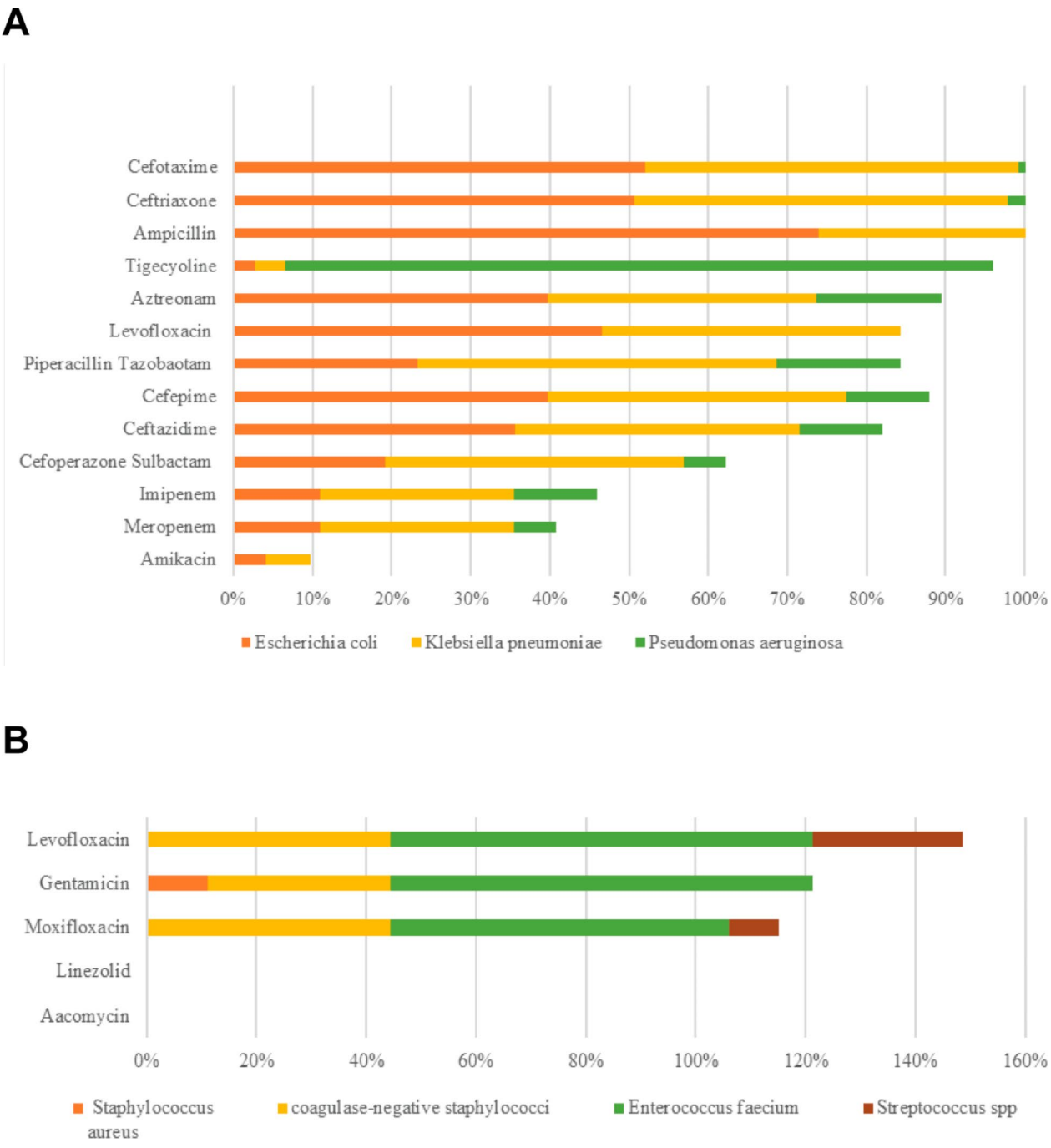

Fig. 3 Analysis of drug resistance in BSIs with gram-negative bacteria among patients with HMs. (**A**) Drug resistance patterns in Gram-negative bacteria causing BSIs. (**B**) Drug resistance patterns in Gram-positive bacteria causing BSIs

showed that both the Logistic and RF models exhibited higher prediction accuracy, confirming their reliability in forecasting 30-day mortality risk in HM patients with BSI (Fig. 5D). Ultimately, the LR model was selected as the optimal model due to its robustness and lower risk of overfitting compared to other models.

The logistic regression model

Logistic regression analysis and 10-fold cross validation were performed on the training set. The results showed that the average AUC for the training set was 0.802 (0.716–0.888), the average AUC for the validation set was 0.792 (0.549–0.989), and the AUC of the test set was 0.822 (0.679–0.965) (Fig. 6A–C). Calibration plots indicated that the 30-day mortality predictions made by

Table 2 Univariate and multivariate logistic regression analyses of 30-day mortality in 231 patients

characteristic	Univariable analysis		Multivariable analysis	
	OR(95%CI)	*P*-value	OR(95%CI)	*P*-value
Gender	1.04 (0.57–1.88)	0.9		
Age ≥ 60 years	1.96 (1.04–3.70)	0.038	2.79 (1.15–6.77)	0.023
Relapsed/refractory HMs	2.00 (1.01–3.93)	0.045	0.52 (0.10–2.86)	0.455
Disease status	0.18 (0.07–0.48)	< 0.001	0.17 (0.05–0.58)	0.004
Polymicrobial BSI	10.39 (3.55–30.38)	< 0.001	14.02 (3.55–55.48)	< 0.001
IL-4 > 2.492pg/ml	2.72 (1.46–5.08)	0.002	3.21 (1.36–7.57)	0.008
IL-10 > 107.46pg/ml	2.46 (1.33–4.57)	0.004	1.23 (0.50–3.04)	0.647
IFN-γ > 7.29pg/ml	1.27 (0.70–2.30)	0.428		
TNF-α > 4.59pg/ml	2.52 (1.36–4.68)	0.003	1.43 (0.59–3.49)	0.429
ALB < 30 g/L	1.84 (1.01–3.38)	0.048	0.99 (0.42–2.31)	0.975
PLT	0.99 (0.98–1.00)	0.016	0.99 (0.97–1.00)	0.05
ALT	1.01 (1.00–1.01)	0.006	0.99 (0.99–1.00)	0.141
AST	1.01 (1.00–1.01)	< 0.001	1.01 (1.00–1.02)	0.003
TB	1.03 (1.01–1.04)	0.002	1.02 (1.00–1.04)	0.083
DB	1.02 (1.00–1.03)	0.022	1.00 (0.98–1.02)	0.774
IL-6	1.00 (1.00–1.00)	0.002	1.00 (1.00–1.00)	0.021
IL-2	1.01 (0.99–1.02)	0.301		
PCT	1.01 (1.00–1.02)	0.267		

the LR model closely aligned with the actual mortality observed (Fig. 6D). On the test set, the model similarly demonstrates good net returns, especially in the range of threshold probabilities from 0.2 to 1.0, where it maintained a high level of net returns (Fig. 6E). The confusion matrix results revealed the model's performance across different datasets. In the training set (Supplementary Fig. 2A), the model correctly identified 92 true negatives and 31 true positives, while misidentifying 26 false positives and 12 false negatives, yielding a true positive rate (sensitivity) of 72.09% and a true negative rate (specificity) of 77.96%. In the test set (Supplementary Fig. 2B), the model correctly identified 47 true negatives and 12 true positives, misidentifying 7 false positives and 4 false negatives, resulting in a true positive rate of 75% and a true negative rate of 87.04%. Given that the performance on the validation set under the AUC index was lower than that of the test set and the ratio was below 10%, the model fitting could be considered successful. The learning curve further indicated strong fitting and high stability between the training and validation sets (Fig. 6F). These results suggest that the LR model is suitable for the classification task on the dataset.

Model interpretation based on SHAP

To assess the relative significance of the selected factors, we employed SHAP values to illustrate how these factors predicted the 30-day mortality risk following BSI in patients with HMs. Figure 7A represents the five most important features in the model. For each feature, the attributions of all patients are plotted, with different colored dots representing varying risk values—red dots indicating high risk and blue dots indicating low risk. The results indicate that higher levels of IL-6, AST, and age > 60 years, along with IL-4 > 2.492 pg/ml and polymicrobial BSI, were associated with an increased risk of 30-day mortality following BSI in HM patients. Figure 7B further illustrates the impact of the top five features, ranked by importance, on the prediction outcomes. The vertical axis represents the individual features in descending order of importance, while the horizontal axis shows the average SHAP values, indicating how each feature influences the model's predictions. To enhance the model's interpretability, we conducted a detailed analysis of two representative samples, as shown in Fig. 7C and D. By visualizing the SHAP values for these specific samples, we were able to discern the impact of each feature on the model's predictions for these cases, providing a clearer understanding of the model's decision-making process for individual patients.

Discussion

BSI is a common and significant prognostic factor in patients with HMs, and identifying key prognostic factors is essential for implementing appropriate treatments. This study included 231 patients with BSIs and analyzed pathogen distribution, antibiotic resistance patterns, and factors predictive of BSI outcomes. A logistic regression model was developed to effectively predict 30-day mortality in BSI patients with HMs. Through careful variable selection and comparison of various ML models, this study underscores the importance of key predictive factors, providing valuable tools for clinical decision-making.

The results revealed that AML and ALL were the most common hematologic malignancies associated with BSIs, emphasizing the need for more proactive infection control measures in patients with acute leukemia. Additionally, patients in the newly diagnosed and relapse/refractory stages exhibited higher rates of BSIs and

Table 3 Baseline characteristics of the training and test cohorts

Variable	Overall, $N=231$[1]	Training cohort, $N=161$[1]	Test cohort, $N=70$[1]	*p*-value[2]
Survival Status, n (%)				0.97
alive	172 (74)	120 (75)	52 (74)	
dead	59 (26)	41 (25)	18 (26)	
Gender, n (%)				0.005
Male	123 (53)	76 (47)	47 (67)	
Female	108 (47)	85 (53)	23 (33)	
Age > 60years, n (%)	62 (27)	43 (27)	19 (27)	0.95
Relapsed/refractory HMs, n (%)	49 (21)	33 (20)	16 (23)	0.69
Basic disease, n (%)	66 (29)	48 (30)	18 (26)	0.53
Disease status, n (%)				0.54
Initial consultation	91 (39)	67 (42)	24 (34)	
CR/PR	79 (34)	54 (34)	25 (36)	
NR/relapse/PD	61 (26)	40 (25)	21 (30)	
Polymicrobial BSI, n (%)	19 (8.2)	13 (8.1)	6 (8.6)	0.90
Pathogens, n (%)				0.52
Gram-negative bacteria	147 (64)	107 (66)	40 (57)	
Gram-positive bacteria	52 (23)	33 (20)	19 (27)	
Fungi	13 (5.6)	8 (5.0)	5 (7.1)	
Polymicrobial BSI	19 (8.2)	13 (8.1)	6 (8.6)	
PLT, Median (IQR)	13.00 (4.00–36.00)	13.00 (4.00–36.00)	14.00 (4.00–32.00)	0.87
ALT, Median (IQR)	22.20 (12.70–50.00)	22.10 (13.20–54.40)	22.20 (11.10–47.20)	0.90
AST, Median (IQR)	22.30 (12.70–40.60)	21.60 (13.40–38.60)	25.75 (11.60–43.10)	0.88
TB, Median (IQR)	15.80 (10.30–24.00)	16.50 (11.60–26.10)	12.45 (8.70–18.70)	0.007
DB, Median (IQR)	7.00 (4.10–11.80)	6.30 (4.10–12.40)	7.05 (4.10–10.90)	0.71
IB, Median (IQR)	7.70 (5.40–13.30)	8.00 (5.30–13.80)	7.45 (5.80–10.00)	0.22
PCT, Median (IQR)	1.57 (0.36–11.42)	2.20 (0.40–12.49)	1.15 (0.26–8.76)	0.16
IL-2, Median (IQR)	3.00 (1.66–5.35)	3.59 (1.74–5.54)	2.48 (1.56–4.88)	0.072
IL-6, Median (IQR)	875.00 (165.71–3,799.88)	780.11 (187.15–3,594.34)	1,108.93 (144.99–3,941.96)	0.99
TNF-α, Median (IQR)	4.59 (2.78–7.37)	4.47 (2.66–8.21)	4.86 (2.92–6.60)	0.75
ALB < 30 g/L, n (%)	81 (35)	56 (35)	25 (36)	0.89
IL-4 > 2.492pg/ml, n (%)	115 (50)	82 (51)	33 (47)	0.60
IL-10 > 107.46pg/ml, n (%)	115 (50)	78 (48)	37 (53)	0.54
IFN-γ > 7.29pg/ml, n (%)	115 (50)	80 (50)	35 (50)	0.97

[1]Median (IQR) or Frequency (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

mortality, whereas those in complete or partial remission experienced lower infection rates and mortality. These findings highlight the critical role of controlling the underlying disease in managing BSIs and improving patient prognosis.

After the occurrence of BSI, prompt and appropriate antimicrobial treatment is necessary, with antibiotic selection tailored to the specific pathogen species and its distribution. In this study, gram-negative bacteria remained the predominant pathogens (63.64%), with *Escherichia coli* (29.25%) being the most common, followed by *Klebsiella pneumoniae* (21.23%) and *Pseudomonas aeruginosa* (8.02%), which is consistent with reports from other centers in China [8]. A retrospective study from 2007 to 2017 reported that Gram-negative bacteremia accounted for 65% of cases, with *Escherichia coli* as the most frequent pathogen [28]. Similarly, a study in China found that Gram-negative bacteria accounted for 64.7% of BSIs in patients with HMs, with *Klebsiella pneumoniae* being the most common, while Gram-positive bacteria accounted for 27.7%, primarily *CoNS* and fungi made up 7.7% [5].In our study, Gram-positive bacteria caused 22.51% of BSIs, with *CoNS* and *Staphylococcus aureus* being the most common pathogens, consistent with other studies [8, 28, 32, 33]. Fungal infections accounted for 5.63%, with *Candida tropicalis* being the predominant pathogen, similar to other reports [8, 32].

Polymicrobial BSI were observed in 8.23% of cases, with 94.74% (18/19) involving two pathogens and one case with three pathogens. Among these, 57.89% (11/19) were combinations of *Escherichia coli* with other Gram-negative bacteria, Gram-positive bacteria, or fungi. Chen

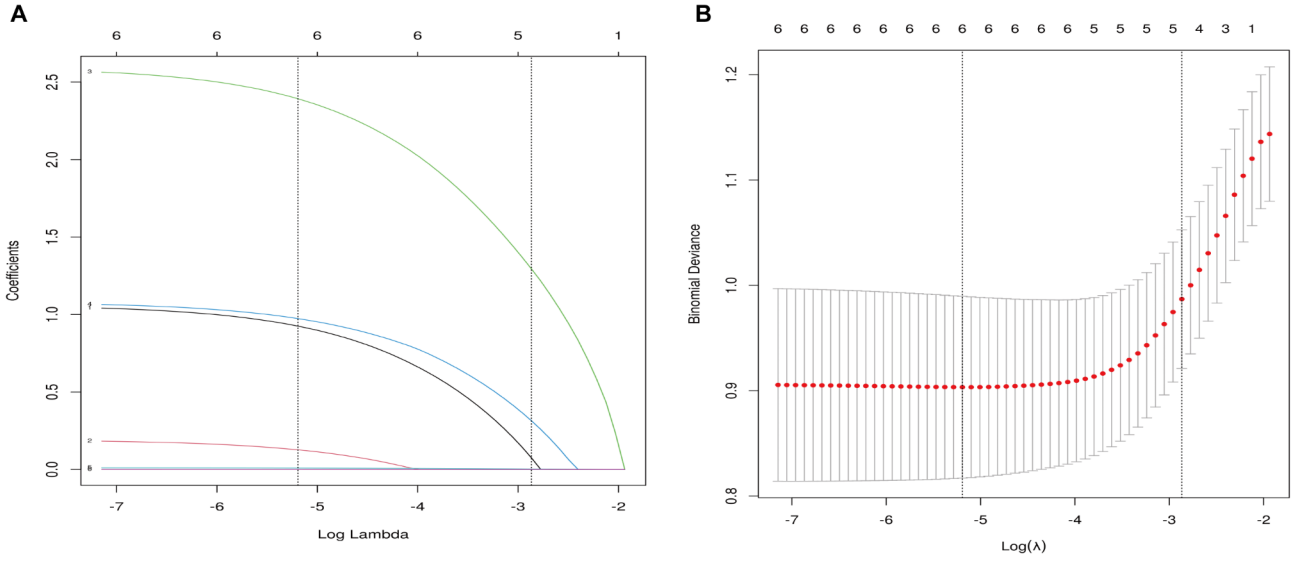

Fig. 4 LASSO regression analysis for feature selection. (**A**) The use of 10-fold cross-validation to select the optimal lambda value, with vertical lines marking the values where six non-zero coefficients are identified. (**B**) Coefficient profiles of six texture features in the LASSO model across the log(λ) sequence. Vertical dotted lines indicate the minimum mean square error (λ = 0.006) and the standard error of the minimum distance (λ = 0.057)

et al. reported a 2.3% incidence of polymicrobial BSI in HM patients [5], while Li et al. found a 2.76% incidence from 2012–2019 [34]. A prospective multicenter study from Italy reported that 14.4% of bacterial BSIs were polymicrobial [3].These findings indicate that the prevalence of gram-positive and gram-negative bacteria is consistent across studies, while the incidence of polymicrobial BSI may vary due to differences in hematologic malignancy types, sample sizes, and regional pathogen distribution. Clinicians should tailor antimicrobial agents based on local pathogen trends to effectively manage BSIs.

Early and effective antimicrobial therapy is critical to reducing mortality in HM patients with BSI. However, due to the low positivity rate and delayed results of blood cultures, empirical therapy remains the primary approach in clinical practice. The widespread use of antibiotics has led to the emergence of resistant strains, which are progressively developing increased resistance, transitioning from low to high resistance and from single-drug to multidrug resistance, complicating empirical treatment. The development of resistance in gram-negative bacteria is mainly associated with the production of β-lactamases, which hydrolyze β-lactam antibiotics, modify antibiotic targets, enhance drug efflux pumps, or decrease the permeability of the outer membrane, leading to resistance [35]. In the context of increasing antibiotic resistance and limited treatment options, understanding local epidemiology and pathogens resistance patterns is essential for selecting the appropriate antibiotics. This study found that common gram-negative bacteria were most sensitive to amikacin, meropenem, imipenem, and piperacillin-tazobactam. *Escherichia coli* exhibited the highest resistance to ampicillin, cefotaxime, and ceftriaxone, with nearly 50% resistance to levofloxacin and 35.62% to ceftazidime. *Klebsiella pneumoniae* showed 24.53% resistance to meropenem and imipenem, 35.85% to ceftazidime, and 45.28% to piperacillin-tazobactam. *Pseudomonas aeruginosa* demonstrated high resistance (89.47%) to ceftriaxone, cefotaxime, and tigecycline, while it remained sensitive to ceftazidime. No resistance to linezolid or vancomycin was detected in gram-positive bacteria; however, MRSA and MRCNS were identified [36]. Fungal infections, particularly *Candida tropicalis*, were also prevalent in HM patients, consistent with other reports from China [8, 32]. Resistance to voriconazole in fungal infections exceeded 50%, suggesting that alternatives such as amphotericin B, caspofungin, or micafungin should be considered for antifungal treatment. Xiao et al. reported a 40.5% mortality rate from fungal BSIs in HMs, which is significantly higher than that of other common fungal infections [37]. Thus, understanding fungal distribution and antifungal resistance is crucial for effective treatment.

BSI is a significant cause of mortality in patients with HMs, with a reported 30-day mortality of 20-30% [2, 4, 5, 8]. In our study, the 30-day mortality was 25.5%. Early identification of prognostic factors and the development of predictive models are crucial for effective management and improving outcomes in HM patients with BSIs. This study explores the predictive factors for BSI outcomes and develops a logistic regression model using ML classification techniques to effectively predict 30-day mortality in these patients. The results identified independent risk factors for 30-day mortality in HM patients, including

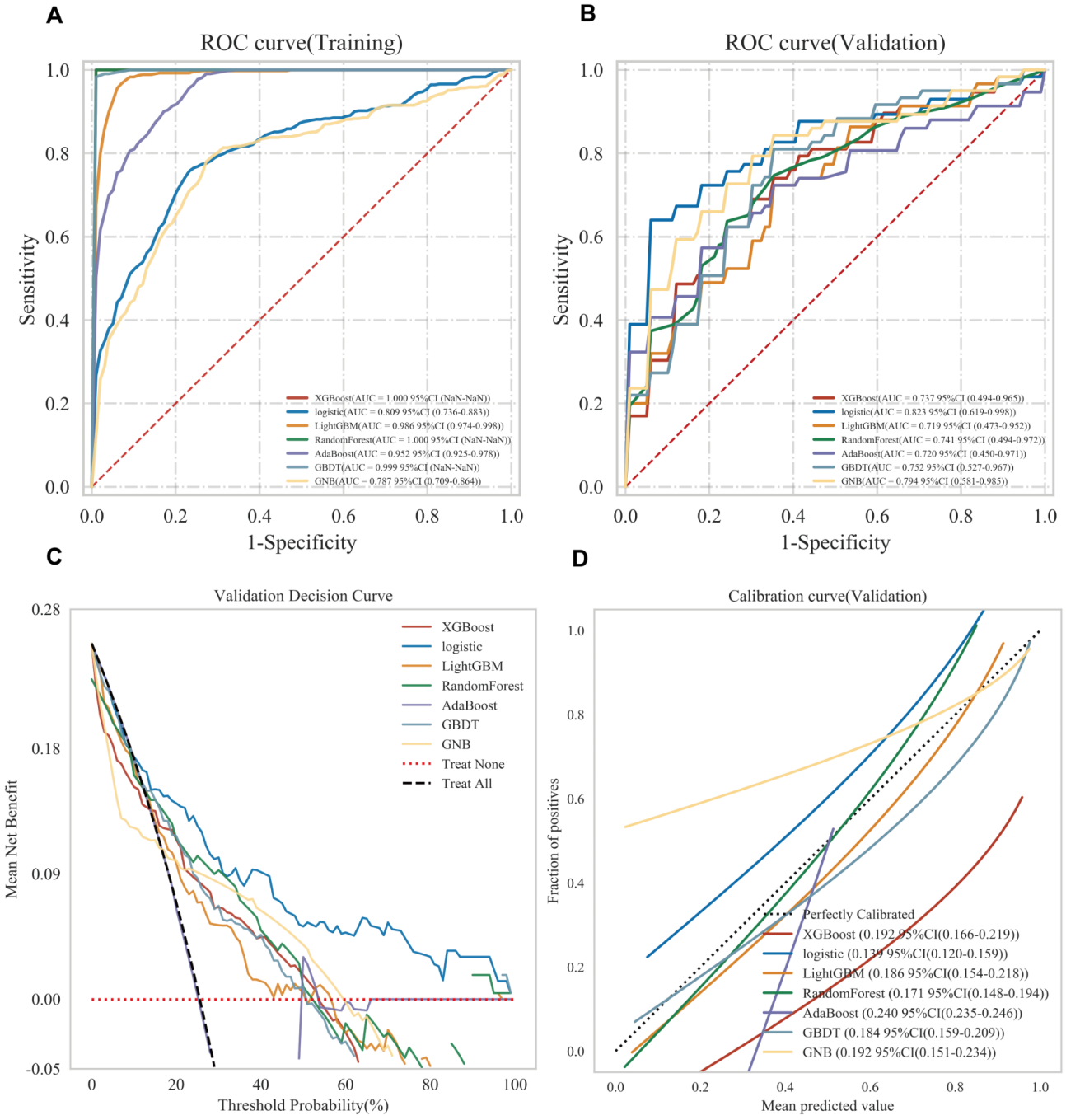

Fig. 5 Comprehensive analysis of the ML Model. (**A**) Area under the receiver operating characteristic curve (AUC) for the training and validation cohorts. (**B**) Patients were sampled 10 times at a 7:3 ratio. (**C**) Decision curve analysis for the validation cohort. (**D**) Calibration curve for the validation cohort

age > 60 years, polymicrobial BSI, IL-4 > 2.492 pg/ml, and elevated IL-6 and AST levels.

Polymicrobial BSIs, though less common than monomicrobial BSIs, are frequently encountered in clinical practice, particularly among patients with HMs. These patients often experience immune suppression due to both the malignancy and treatments such as chemotherapy, targeted therapy, immunotherapy, or bone marrow transplantation.This immunocompromised state increases susceptibility to infections caused by multiple pathogens, resulting in polymicrobial BSIs that present complex clinical challenges. While few studies have explored the impact of polymicrobial BSIs on the prognosis of HM patients, our study found that polymicrobial infections are a significant risk factor for 30-day mortality. These infections complicate clinical management

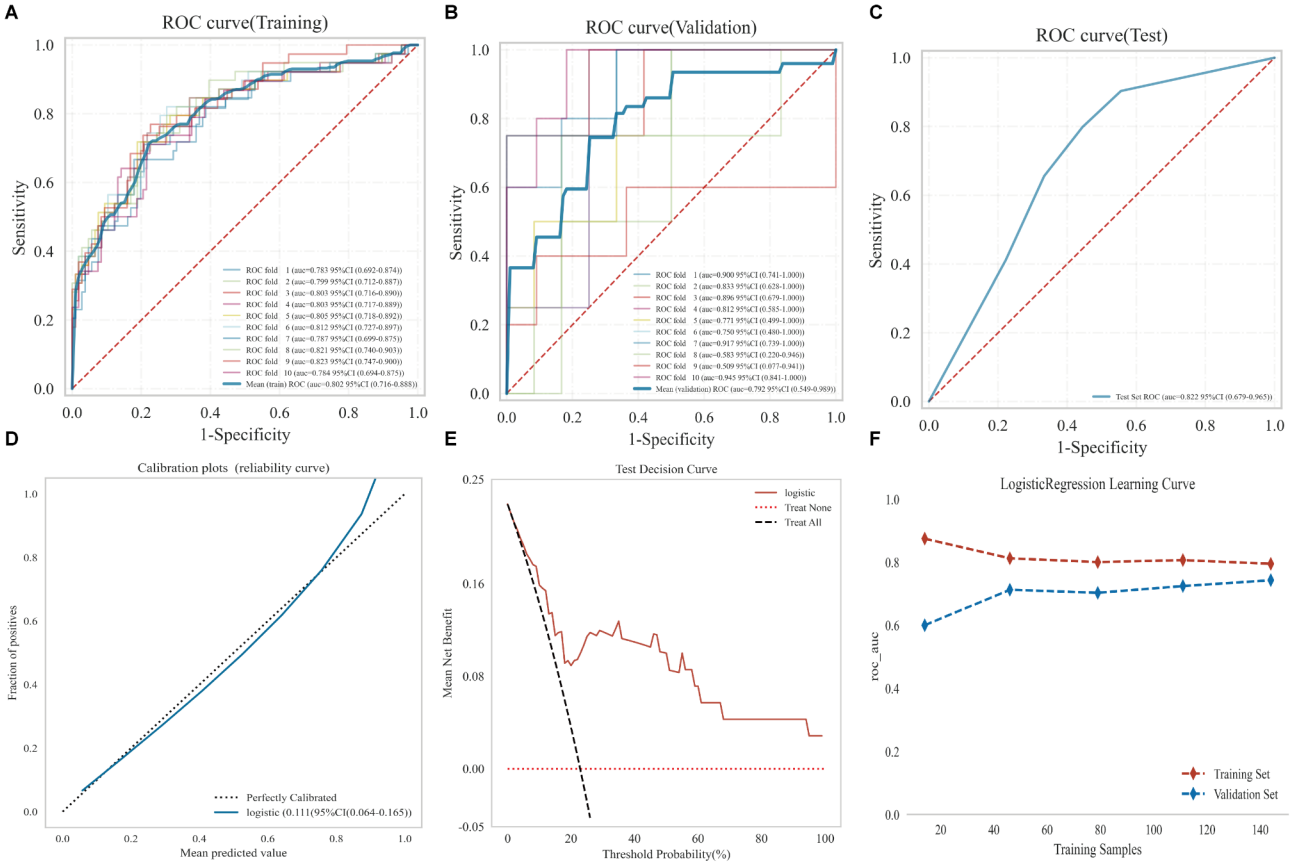

Fig. 6 Comprehensive evaluation of the logistic regression model. (**A**) ROC and AUC for the training and the validation cohorts. (**B**). (**C**) ROC and AUC for the test cohort. (**D**) Calibration curve for the test cohort. (**E**) Decision curve analysis for the test cohort. (**F**) Learning curve for the LR model

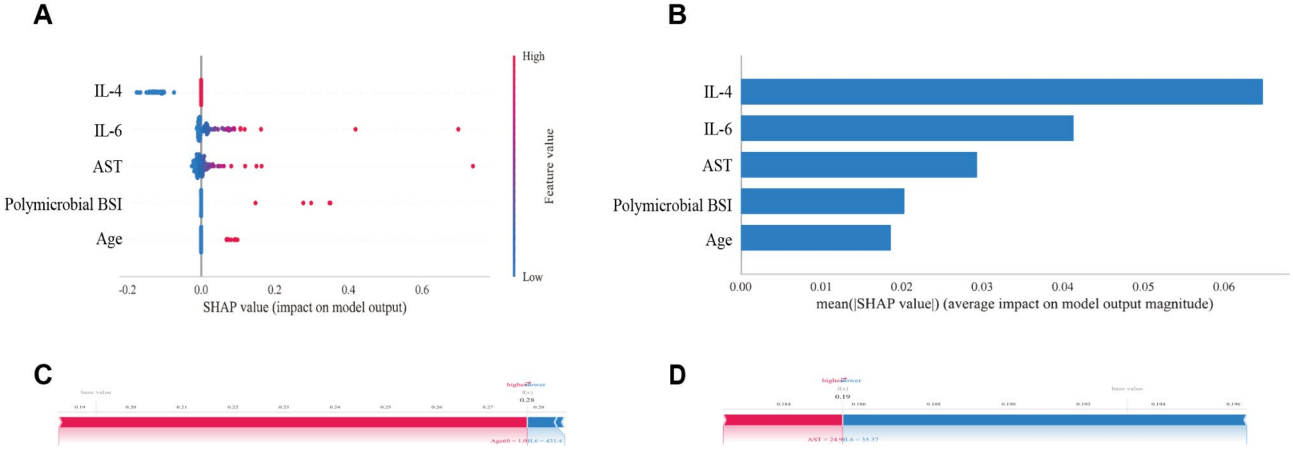

Fig. 7 SHAP Interpretation of the Model. (**A**) SHAP values for the selected features in the model. (**B**) Feature importance ranking based on SHAP values. (**C, D**) Detailed SHAP interpretability analysis for two independent samples

because treatment decisions must account for the resistance profiles of multiple pathogens. For example, when *Escherichia coli* combined with *Klebsiella pneumoniae*, the latter's resistance to carbapenems may limit treatment options, reducing the efficacy of carbapenem-based therapies. Additionally, combinations of *Escherichia coli* and gram-positive cocci (e.g., Enterococcus species) may occur, necessitating combination therapy—such as carbapenems paired with vancomycin or linezolid—to ensure adequate coverage of both pathogens. However, this can lead to potential drug interactions, which require careful monitoring. Given the complexity of polymicrobial BSIs, a comprehensive, individualized treatment

approach is crucial for improving outcomes and reducing mortality in HM patients.

Th1 and Th2 cells play distinct roles in immune responses: Th1 cells secrete IL-2, IFN-γ, and TNF-α to drive cellular immunity, while Th2 cells mediate humoral immunity by stimulating B cell proliferation and releasing cytokines like IL-4, IL-6, and IL-10. Disruptions in the balance of Th1/Th2 responses can occur in infections, tumors, and autoimmune diseases. Cytokines, due to their critical role in immune responses, have emerged as important diagnostic biomarkers for infections [38]. Studies have demonstrated that IL-6 are useful diagnostic markers for bacteremia in both pediatric and adult hematologic patients [14, 17, 20]. In particular, IL-6 have shown predictive value for severe infections in pediatric hematologic patients [20].Zhang L et al. [18] found that levels of IL-6 were elevated in newly diagnosed Non-Hodgkin Lymphoma patients with respiratory infections compared to those without infections. Specifically, IL-6 levels ≥ 102.6 pg/mL were indicative of bacterial lung infection with bacteremia. However, few studies have investigated the prognostic value of Th1/Th2 cytokines in HMs with BSI. IL-4 and IL-6 play critical roles in immune regulation and inflammatory responses, which may influence the prognosis of BSI in HMs. Our study identifies IL-4 and IL-6 as independent risk factors for 30-day mortality following BSI in HM patients. IL-4, a Th2 cytokine, is primarily involved in anti-inflammatory responses and immune modulation, potentially affecting the host's ability to clear infections. In contrast, IL-6 is a well-established pro-inflammatory cytokine that contributes to the acute-phase response and systemic inflammation, which are closely linked to sepsis severity and poor outcomes in immunocompromised patients [15]. Furthermore, excessive IL-4 and IL-6 levels can trigger an overactive immune response, causing inflammatory damage and multi-organ dysfunction. Given these findings, routine monitoring of Th1/Th2 cytokines in HM patients with BSI is recommended. Patients with elevated IL-4 and IL-6 levels should be closely monitored for signs of organ dysfunction and receive prompt treatment to prevent complications. Proactive immune modulation may help reduce mortality and improve outcomes.

Our study also highlighted the significant association between elevated AST levels and 30-day mortality following BSI in HM patients. AST, an enzyme found primarily in the liver, heart, and kidneys, is released into the bloodstream when these organs are damaged. In the context of BSI, apoptosis, metabolic disturbances, and mitochondrial dysfunction can cause multi-organ injury. Specifically, BSI-induced damage may impair cardiac function, reduce myocardial contractility, and decrease cardiac output, leading to pulmonary and systemic congestion, as well as insufficient organ perfusion [39]. Additionally, microcirculatory dysfunction in the kidneys can cause tubular cell dysfunction and apoptosis, contributing to acute kidney injury [40]. Given the critical role of AST as an indicator of organ dysfunction, routine monitoring of AST levels should be incorporated into the clinical management of HM patients with BSI. This will enable early detection of organ damage and guide appropriate therapeutic interventions to protect organ function during anti-infective therapy. By closely monitoring AST and other relevant biomarkers, clinicians can better manage the risk of multi-organ dysfunction and improve patient outcomes in this high-risk population.

Despite its strengths, our study has certain limitations. First, as a retrospective study, selection bias is an inherent limitation. Patient inclusion was based on pre-existing medical records, which may not fully represent the broader population. To minimize this bias, we applied strict inclusion and exclusion criteria, ensuring that only patients meeting well-defined diagnostic standards were included. Additionally, appropriate imputation techniques were used to handle missing values. Second, our study only included internal validation, which may limit the generalizability of the model. External validation using independent datasets, as well as prospective studies, will be necessary to further refine and confirm our findings. Third, potential heterogeneity within the patient population exists due to the diverse nature of hematologic malignancies, which may influence the model's performance across different subgroups. Finally, as a single-center study, our results may be subject to regional variations. Multi-center studies will be required to validate our findings and enhance the generalizability of our model.

Conclusion

We identified age > 60 years, polymicrobial BSI, IL-4 > 2.492 pg/mL, IL-6 and AST levels as independent risk factors for 30-day mortality in HMs with BSI. Based on these factors, we developed and validated a logistic regression prediction model with strong predictive accuracy. The model, incorporating easily accessible clinical indicators, aids in the early identification of high-risk patients, facilitating optimized management and timely interventions to reduce disease progression and BSI-related mortality in this patient population.

Abbreviations

BSI	Bloodstream infection
HM	Hematologic malignancies
XGBoost	Xtreme Gradient Boosting
LR	Logistic Regression
LightGBM	Light Gradient Boosting Machine
RF	RandomForest
AdaBoost	Adaptive Boosting
GBDT	Gradient Boosting Decision Tree
GNB	Gaussian Naïve Bayes
ROC	Receiver operating characteristic curve

SHAP	Shapley Additive Explanations
MDR	Multidrug-resistant
IL-2	Interleukin-2
IFN-γ	Interferon-gamma
TNF-α	Tumor necrosis factor-alpha
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
ML	Machine learning
HLH	Hemophagocytic Syndrome
CoNS	Coagulase-negative staphylococci
PCT	Procalcitonin
Crea	Creatinine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALB	Serum albumin
TB	Total bilirubin
DB	Direct bilirubin
IB	Indirect bilirubin
LASSO	Least Absolute Shrinkage and Selection Operator
CI	Confidence intervals
OR	Odds ratios
RCS	Restricted cubic spline
AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia
MDS	Myelodysplastic syndromes
MM	Multiple Myeloma
CRE	Carbapenem resisant enterbacteriaceae
MRSA	Methicillin-resistant Staphylococcus aureus
MRCNS	Methicillin-resistant coagulase-negative staphylococcus
AUC	Area under the curve
DCA	Decision curve analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10808-7.

Supplementary Material 1

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Author contributions
Qin Li and Nan Lin collected cases and wrote the main manuscript. Zuheng Wang and Yuexi Chen analyzed the data. Yuli Xie drew the picture. Xuemei Wang and Jirui Tang collected the data. Yuling Xu and Min Xu interpreted the data. Na Lu, Yiqian Huang, and Jiamin Luo completed the tables. Li Jing and Zhenfang Liu designed the study and critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability
The datasets generated and/or analyzed are not publicly available owing to ethical and legal causes. Nevertheless, they can be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research project was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (KY2024541) and conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Affiliated Hospital of Southwest Medical University approved this study protocol and waived the obligation for informed consent because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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