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Original Article

Pediatric sequential organ failure assessment score predicts prognosis in children with acute lymphoblastic leukemia and sepsis: association with early multiple organ dysfunction

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Abstract: Objective: To systematically analyze the clinical characteristics and prognostic factors of children with acute lymphoblastic leukemia (ALL) complicated by sepsis, and to compare the predictive efficacy of different scoring systems, with the expectation of providing a basis for early clinical identification of high-risk patients. Methods: A retrospective analysis was conducted on the clinical data of 260 children with ALL who were admitted to the hospital due to sepsis during chemotherapy. Based on their outcomes after admission to the PICU, they were divided into survival (n=184) and death (n=76) groups. General information, disease status at PICU admission, laboratory indicators, and treatment were collected. Univariate logistic regression analysis was used to identify associated factors of mortality, and the predictive efficacy of different scoring systems for prognosis was compared. Results: Bloodstream infection (29.23%), pulmonary infection (27.69%), and multiple site infection (23.46%) were the main infection sites, with bacterial infection being the predominant pathogen (48.85%). Clinical risk classification was predominantly high-risk (45.77%) and intermediate-risk (41.54%), with an overall PICU mortality rate of 29.23%. Univariate logistic regression analysis showed that leukemia remission status (PR/NR), inflammatory markers (CRP, PCT, IL-6), and organ function-related indicators (ALT, AST, TBiL, Scr, BUN, cTnI, CK-MB, BNP) within 48 hours of PICU admission were statistically correlated with mortality (all $P<0.05$). Furthermore, 24-hour lactate clearance and PaO_2/FiO_2 were negatively correlated with mortality (OR<1, $P<0.05$). ROC curve analysis showed the AUCs for predicting mortality were 0.751, 0.788, and 0.885, respectively, based on the Pediatric Critical Illness Score, Pediatric Early Warning Score, and Pediatric Sequential Organ Failure Assessment Score (PSOFA), with PSOFA showing the highest predictive efficacy. Conclusion: Children with ALL complicated by sepsis, characterized by bloodstream infection, pulmonary infection, multiple site infection, and intermediate-to-high-risk subtypes, have a higher risk of death upon admission to the PICU. Leukemia remission status, 24-hour lactate clearance, inflammatory response, organ function, and respiratory function indicators within 48 hours of PICU admission are closely related to prognosis. Multidimensional indicators combined with a clinical scoring system can help identify high-risk children early and optimize the timing of PICU intervention, thereby improving prognosis.

Keywords: Children, acute lymphoblastic leukemia, sepsis, clinical characteristics, prognosis

Introduction

Acute lymphoblastic leukemia (ALL), a common pediatric hematological malignant tumor, has the highest incidence, accounting for more than 70% of pediatric acute leukemias [1, 2]. With the development of genomics, the diagnosis of ALL has gradually shifted from morphology to genetics and molecular science. The application of targeted drugs based on gene mutations and karyotype results, coupled with the standardization of chemotherapy regimens and advances in supportive treatment, has enabled the overall survival rate of pediatric ALL to reach over 80% [3]. However, more and more studies have pointed out that chemotherapy drugs can strongly inhibit bone marrow hematopoiesis and greatly reduce the body's

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ability to clear pathogens. Therefore, children with ALL have a higher risk of infection during chemotherapy [4]. Moreover, the widespread use of central venous catheters for chemotherapy drug infusion and intravenous nutritional support further aggravates the susceptibility to infection. It also increases the risk of children requiring emergency admission to the Pediatric Intensive Care Unit (PICU) for supportive care due to sudden deterioration during treatment [5]. The 9th Online Conference of the European Association for the Study of Infection in Leukemia highlights that when patients with acute leukemia receive treatments such as targeted drugs and biological therapies, they may develop infectious complications due to the immunosuppressive effects of drugs, increasing the risk of poor prognosis [6]. Gao et al. and Gundluru et al. found that sepsis was one of the common complications during chemotherapy for children with acute leukemia [7, 8]. More than 30% of children are transferred to PICU due to sepsis, which is one of the important causes of death in children with ALL [9]. Therefore, improving the survival rate of children with ALL complicated by sepsis who are transferred to the PICU is the key to improving the overall prognosis of children with ALL.

Studies have found that due to immunosuppression in children with ALL, clinical symptoms when complicated by sepsis usually lack typicality, and stages of sepsis progression vary among different children [10]. Some children do not have typical high fever, but only show hypothermia, lethargy, shortness of breath or accelerated heart rate, which can be easily confused with adverse reactions to chemotherapy drugs, leading to delayed early diagnosis [10]. Therefore, reasonable and effective assessment of changes in the condition of children with ALL complicated by sepsis is an important step in reducing delays in transferring children to PICU for supportive treatment and improving their prognosis. However, these children have complex underlying diseases and rapid disease progression. Their clinical status and disease severity at PICU admission differ significantly, with marked prognostic heterogeneity. Thus, the early identification of high-risk patients remains a major clinical challenge.

At present, the condition assessment criteria for these children who are transferred to the PICU have not yet been unified. Common clinical scoring systems used to assess the clinical status and severity of children include Pediatric Critical Illness Score (PCIS), Pediatric Early Warning Score (PEWS), Pediatric Sequential Organ Failure Assessment (PSOFA) Score, etc. If the above clinical scoring systems are applied to these children, the effect of the application will be evaluated, and the most suitable scoring system for evaluating the condition of them will be found, which will help timely transfer children whose condition changes to the PICU, thereby improving the prognosis. Based on the above background, we retrospectively analyzed the clinical data of children with ALL complicated by sepsis who were admitted to the PICU. We systematically evaluated their clinical characteristics and prognosis-related factors, and compared the association and discriminatory ability of different clinical scoring systems with patient outcomes. This study aimed to provide a reference for the early identification of high-risk children and the rational formulation of treatment strategies in clinical practice.

Materials and methods

General information

A total of 260 children with ALL transferred to the PICU of West China Second University Hospital, Sichuan University, due to sepsis during chemotherapy from October 2020 to October 2025 were enrolled in this single-center, retrospective cohort study.

Clinical data were retrieved from the PICU medical record system, inpatient medical record system, and laboratory system. Initially eligible cases were identified by searching keywords including acute lymphoblastic leukemia, ALL, sepsis and PICU. The final eligibility of each case was independently verified by two researchers.

Inclusion criteria: (1) Meeting the diagnostic criteria for ALL in the revised classification criteria for myeloid tumors and acute leukemia issued by the World Health Organization, and diagnosed with ALL through bone marrow cell morphology and other examinations [11]; (2) Receiving chemotherapy in the pediatric hematology and oncology department, suffer from sepsis during treatment, and meeting the diagnostic criteria for sepsis issued by the International Pediatric Sepsis

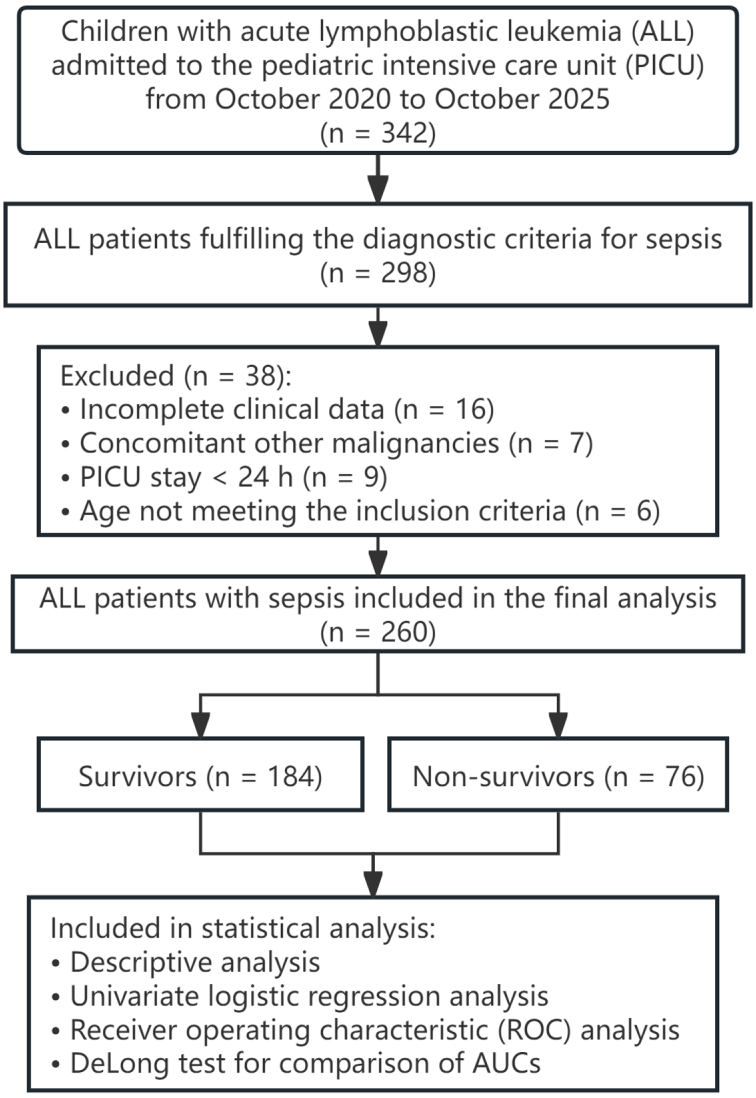

Figure 1. Flow chart of enrollment of children with ALL complicated by sepsis. ALL, acute lymphoblastic leukemia; PICU, pediatric intensive care unit.

Consensus Conference [12]; (3) Age 28 days to 14 years old; (4) requiring transfer to PICU for supportive treatment; (5) Treated in accordance with the China Children's Cancer Group Acute Lymphoblastic Leukemia 2020 protocol (CCCG-ALL-2020); (6) Complete clinical data.

Exclusion criteria: (1) Clinically diagnosed with other hematological diseases or other types of leukemia; (2) Complicated with other non-septic complications and transferred to PICU for treatment; (3) Transferred to PICU from outpatient clinics or out-of-hospital; (4) Abandoning treatment or transferring to another hospital midway.

The specific inclusion process is shown in **Figure 1**.

Ethical statement

This study complies with the principles of the Declaration of Helsinki and has been reviewed and approved by the Medical Ethics Committee of West China Second University Hospital, Sichuan University. As a retrospective cohort study, only data derived from routine clinical diagnosis and treatment were collected. No additional interventions were implemented on the children, and all data were anonymized before analysis. The privacy and personal information of the children and their legal guardians were fully protected.

Data extraction and variable definition

Grouping method: Children were divided into survival (n=184) and death (n=76) groups based on their outcomes after transferred to PICU.

General data: A standardized general information questionnaire was designed according to the research objectives. Relevant information was independently extracted from the electronic medical record system by two researchers, and any discrepancies were resolved through discussion with a third researcher. A general information questionnaire was designed according to the research purpose, including gender, age, height, weight, and clinical risk classification [assessed based on the 'Guidelines for the Diagnosis and Treatment of Childhood Acute Lymphoblastic Leukemia (Fourth Revision)', including standard risk (SR), intermediate risk (IR), and high risk (HR)] [13].

Disease status when transferred to PICU: The following conditions were recorded: length of hospital days before PICU transfer, neutropenia duration (absolute neutrophil count <0.5×10^9/L), and fever duration when they were transferred to the PICU, the site of infec-

tion [including bloodstream infection, pulmonary infection, skin and soft tissue infection, gastrointestinal infection, multi-site infection (i.e., infection sites ≥2), no infection focus found], leukemia remission status within 48 hours after PICU transfer [evaluated with reference to CCCGALL2020, including complete remission (CR), partial remission (PR) and non-remission (NR)], infection type [no clear pathogen, bacterial infection (Gram-negative bacteria, Gram-positive bacteria), fungal infection], invasive mechanical ventilation (yes, no), inotropic drug support (yes, no) [14].

Laboratory indicators when transferred to PICU: The following indicators were recorded: inflammatory indicators [C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6)], immune function indicators [immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), T lymphocyte subsets ($CD4^+/CD8^+$)]; 24-hour lactate clearance rate and organ function indicators including liver function indicators [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL)], renal function indicators [serum creatinine (Scr), blood urea nitrogen (BUN)], cardiac function indicators [cardiac troponin I (cTnI), creatine kinase isoenzyme (CK-MB), B-type brain natriuretic peptide (BNP)], respiratory function indicators [arterial oxygen partial pressure/inhaled oxygen concentration (PaO_2/FiO_2)].

Scores from different scoring systems when transferred to PICU: PCIS, PEWS, and PSOFA when the children in two groups transferred to PICU were compared [15-17].

The PCIS includes 10 physiological indicators such as heart rate, blood pressure, and respiration. Scores of 80 to 100, 71 to 79, and ≤70 represent non-critical, critical, and extremely critical conditions, respectively. The PEWS includes 3 physiological indicators (behavior, cardiovascular system, respiratory system). Each indicator is scored from 0 to 3 points according to the severity degree. The total score ranges from 0 to 9 points. Scores of 0 to 2 points, 3 to 4 points, and ≥5 points respectively represent low, intermediate, and high risks of the disease. PSOFA assesses 6 organ systems (respiratory, coagulation, liver, cardiovascular, central nervous system, renal), each scored 0-4, with a total score of 0-24. Higher scores indicate more severe organ failure and a higher risk of death.

Outcome measures

The primary outcome measure of this study was the outcome of children admitted to the PICU. Secondary outcome measures included PICU length of stay, use of invasive mechanical ventilation, use of positive inotropic drugs, and impairment of major organ function.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. Measurement data that conform to normal distribution are described using ($\chi \pm SD$). Homogeneous variances were analyzed via the independent-samples t-test (intergroup) and paired-samples t-test (intragroup), while heterogeneous variances were assessed using corrected t-test. Categorical data were expressed as counts and percentages and analyzed using the chi-square (χ^2) test.

To analyze the influencing factors on the prognosis (survival = 0, death = 1) of children with ALL complicated by sepsis, univariate analysis was performed on candidate variables. Variables with $P<0.10$ in the univariate analysis and those considered clinically significant were included in the multivariate logistic regression model. Since variables such as invasive mechanical ventilation and inotropic drug support were treatment measures, their use may be influenced by the disease severity, leading to confounding indications. Therefore, they were only used to describe the severity of the child's disease and were not included in the multivariate analysis. For indicators with potential collinearity (such as multiple organ function indicators), only representative variables were selected for the model. The multivariate logistic regression analysis reported the odds ratio (OR) and 95% confidence interval (95% CI). Due to complete or near-complete dissociation between some variables and the outcome, the final results of the multivariate logistic regression analysis were not reported.

The receiver operating characteristic (ROC) curve was used to evaluate the predictive performance of the PCIS, PEWS, and pSOFA scores for mortality in children with ALL complicated by sepsis. The area under the curve (AUC) and its 95% CI were calculated. The DeLong non-parametric test was adopted to compare the AUC values among different scoring systems and assess statistical differ-

Table 1. Clinical characteristics

Clinical Characteristics			Number of cases (n)	Percentage (%)
Infection Site	Bloodstream infection		76	29.23
	Pulmonary infection		72	27.69
	Skin and soft tissue infection		6	2.31
	Gastrointestinal tract infection		20	7.69
	Multisite infection		61	23.46
	Unidentified infection focus		25	9.62
Infection Type	No definite pathogen		128	49.23
	Bacterial infection	Gram-negative bacteria	77	29.62
		Gram-positive bacteria	50	19.23
	Fungal infection		5	1.92
Clinical Risk Stratification	ALL (SR)		33	12.69
	ALL (IR)		108	41.54
	ALL (HR)		119	45.77

Note: ALL, acute lymphoblastic leukemia; SR, standard risk; IR, intermediate risk; HR, high risk.

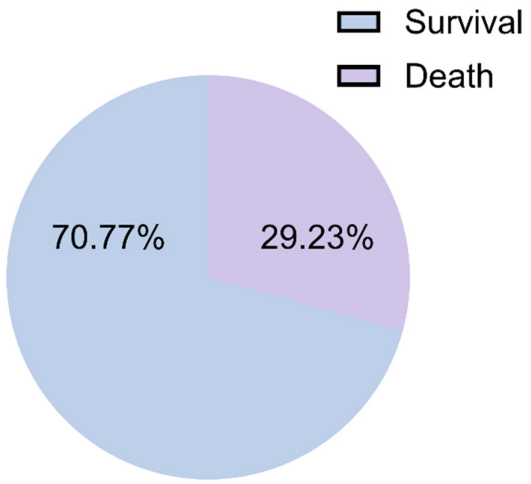

Figure 2. Distribution of survival and death rates in children with ALL complicated with sepsis after PICU admission. ALL, acute lymphoblastic leukemia; PICU, pediatric intensive care unit.

ences in discriminatory ability between predictive models.

The diagnostic efficacy of AUC was interpreted according to the following criteria: AUC>0.90 indicated excellent predictive performance; an AUC of 0.71-0.90 indicated good predictive ability; an AUC of 0.50-0.70 indicated limited predictive ability; and AUC<0.50 suggested no predictive value. ROC curve plotting and calculations of AUC with 95% CI were performed using MedCalc software.

Since the ROC curves of different scoring systems were derived from the same cohort and regarded as correlated samples, pairwise comparisons of AUCs for correlated ROC curves were conducted via the DeLong test. The difference in AUC (ΔAUC) and its standard error were calculated to obtain the 95% CI and *P*-values for evaluating differences in predictive efficacy across scoring systems. All statistical tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

Results

Clinical characteristics

From the perspective of infection site, 235 of the 260 children with ALL complicated by sepsis in this study had clear infection sites, mainly bloodstream infection, pulmonary infection and multi-site infection, accounting for 29.23%, 27.69% and 23.46% respectively. In terms of infection types, 128 of the 260 children had no clear pathogen, accounting for 49.23%, 132 cases were pathogen-positive, mainly bacterial infections, accounting for 48.85% (of which Gram-negative bacteria accounted for 29.62% and Gram-positive bacteria accounted for 19.23%). In terms of clinical risk classification, the proportion of ALL (HR) and ALL (IR) accounted for a higher proportion, at 45.77% and 41.54% respectively. See **Table 1**.

Table 2. Comparison of baseline data

Variables		Survival group (n=184)	Death group (n=76)	t/χ^2	P
Gender, n (%)	Male	102 (55.43)	36 (47.37)	χ^2=1.405	0.236
	Female	82 (44.57)	40 (52.63)		
Age (Mean ± SD, years)		4.38±2.81	4.41±2.77	*t*=0.786	0.937
Length of hospital stay at PICU admission, n (%)	≤14 d	117 (63.59)	39 (51.32)	χ^2=3.375	0.066
	>14 d	67 (36.41)	37 (48.68)		
Duration of neutropenia at PICU admission, n (%)	≤7 d	89 (48.37)	31 (40.79)	χ^2=1.244	0.265
	>7 d	95 (51.63)	45 (59.21)		
Duration of fever at PICU admission, n (%)	≤7 d	143 (77.72)	52 (68.42)	χ^2=2.479	0.115
	>7 d	41 (22.28)	24 (31.58)		

Note: PICU, pediatric intensive care unit.

Prognosis of children with ALL complicated by sepsis

In this study, 260 children with ALL complicated by sepsis were transferred to the PICU. Among them, 184 survived (70.77%) and 76 died (29.23%). See **Figure 2**.

Comparison of baseline data

In terms of general baseline data, there were no statistically significant differences between the survival and death groups in terms of gender composition, age, length of hospital stays when transferred to PICU, neutropenia duration or fever duration (all P>0.05). These results suggest that the two groups of children are comparable. See **Table 2**.

Comparison of clinical status and inflammatory response indicators

Within 48 hours after transferred to PICU, there was a significant difference in leukemia remission status between the groups (P<0.05). Incomplete remission of leukemia was more common in the death group than that in the survival group (P<0.05). There were significant differences in the levels of inflammation and infection-related biomarkers, including CRP, PCT, and IL-6, between the two groups of children, and the above indicators were significantly increased in the death group (all P<0.05). See **Table 3**.

Comparison of immune function indicators

The levels of IgG, IgA and IgM in the survival group were slightly higher than those in the death group, while the $CD4^+/CD8^+$ ratio was slightly lower in the death group, but the overall difference was not statistically significant (all P>0.05). The results suggested that the baseline immune function in terms of humoral and cellular immunity were basically consistent between the two groups and had no significant impact on prognosis. See **Table 4**.

Comparison of respiratory support, circulatory support and tissue perfusion status

The death group received invasive mechanical ventilation and inotropic drug support more frequently after transfer to the PICU, but the differences between the two groups were not statistically significant (both P>0.05). The 24-hour lactate clearance rate in the death group was significantly lower than that in the survival group (P<0.001), reflecting the poor ability of the death group to improve tissue perfusion and metabolism. See **Table 5**.

Comparison of liver and kidney function indicators

The liver function indicators (ALT, AST, TBiL) and renal function indicators (Scr, BUN) in the death group were significantly higher than those in the survival group (all P<0.05), indicating more pronounced liver and kidney damage. See **Figure 3**.

Comparison of myocardial injury indicators and oxygenation function indicators

The myocardial injury markers cTnI, CK-MB, and BNP in the death group were significantly

Table 3. Comparison of clinical status and inflammatory response indicators

Variables		Survival group (n=184)	Death group (n=76)	t/χ^2	P
Remission status of leukemia within 48 hours after PICU admission n (%)	CR	125 (67.93)	30 (39.47)	χ^2=18.096	<0.001
	PR/NR	59 (32.07)	46 (60.53)		
Infection site n (%)	Bloodstream infection	48 (26.09)	24 (31.58)	χ^2=1.405	0.843
	Pulmonary infection	57 (30.98)	19 (25.00)		
	Infection in other sites	17 (9.24)	8 (10.53)		
	Multisite infection	43 (23.37)	18 (23.68)		
	Unidentified infection focus	19 (10.33)	7 (9.21)		
CRP ($\bar{x}\pm s$, mg/L)		80.39±7.16	98.93±8.57	t=17.898	<0.001
PCT ($\bar{x}\pm s$, ng/mL)		6.12±0.73	8.39±0.78	t=22.350	<0.001
IL-6 ($\bar{x}\pm s$, pg/mL)		174.79±13.46	232.87±20.29	t=27.038	<0.001

Note: PICU, pediatric intensive care unit; CR, complete remission; PR, partial remission; NR, no remission; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6.

Table 4. Comparison of immune function indicators

Variables	Survival group (n=184)	Death group (n=76)	t/χ^2	P
IgG ($\bar{x}\pm s$, g/L)	9.92±2.15	9.64±2.03	t=0.971	0.333
IgA ($\bar{x}\pm s$, g/L)	2.57±0.24	2.54±0.22	t=0.939	0.349
IgM ($\bar{x}\pm s$, g/L)	0.67±0.15	0.65±0.13	t=1.015	0.311
$CD4^+/CD8^+$ ($\bar{x}\pm s$)	1.14±0.11	1.12±0.10	t=1.368	0.172

Table 5. Comparison of respiratory support, circulatory support and tissue perfusion status

Variables		Survival group (n=184)	Death group (n=76)	t/χ^2	P
Invasive mechanical ventilation n (%)	No	59 (32.07)	17 (22.37)	χ^2=2.445	0.118
	Yes	125 (67.93)	59 (77.63)		
Positive inotropic drug support n (%)	No	141 (76.63)	51 (67.11)	χ^2=2.527	0.112
	Yes	43 (23.37)	25 (32.89)		
24-hour lactate clearance ($\bar{x}\pm s$, %)		37.56±4.62	23.78±3.41	t=23.483	<0.001

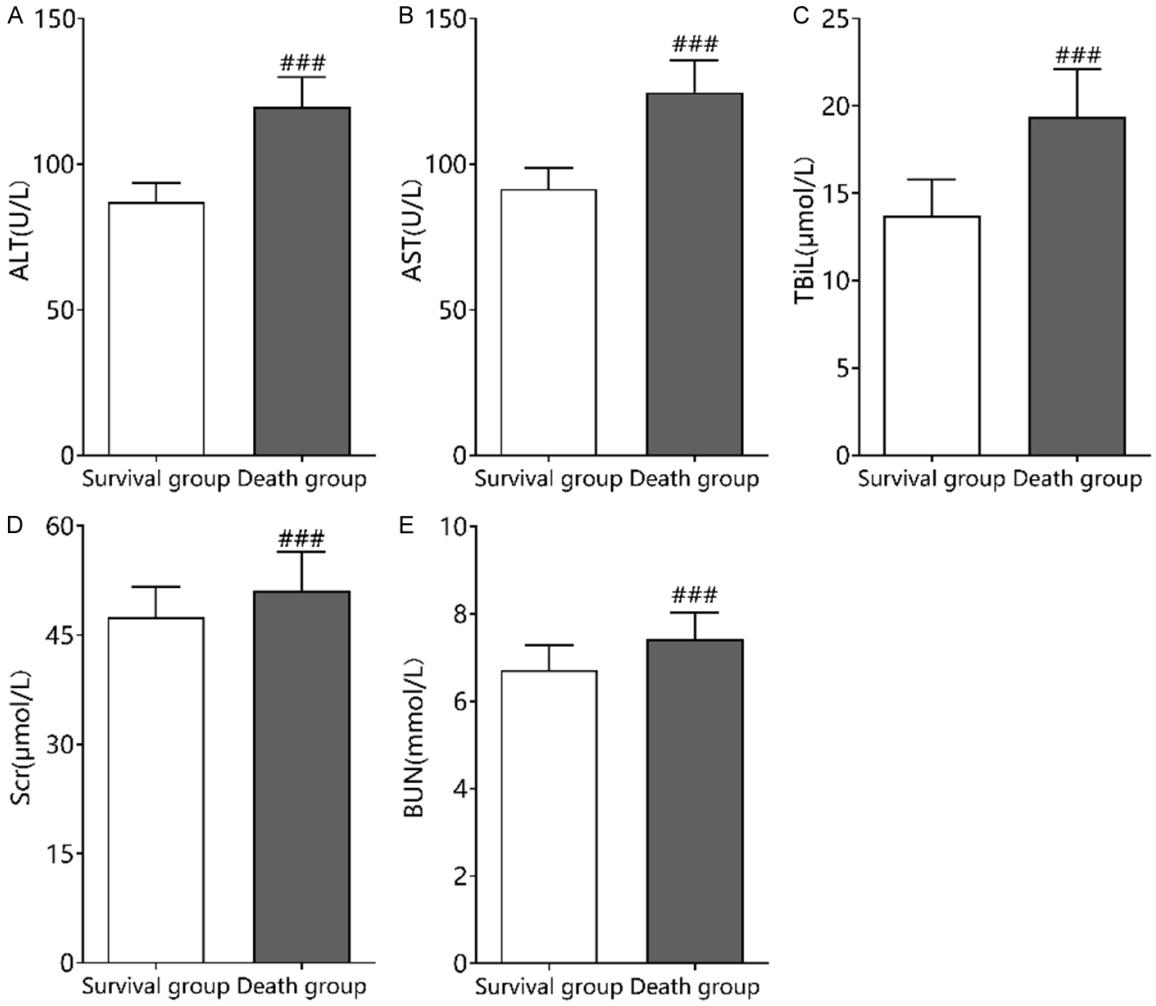

Figure 3. Comparison of liver and kidney function indicators. A. ALT; B. AST; C. TBiL; D. Scr; E. BUN. Compared with the survival group, ###P<0.001. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen.

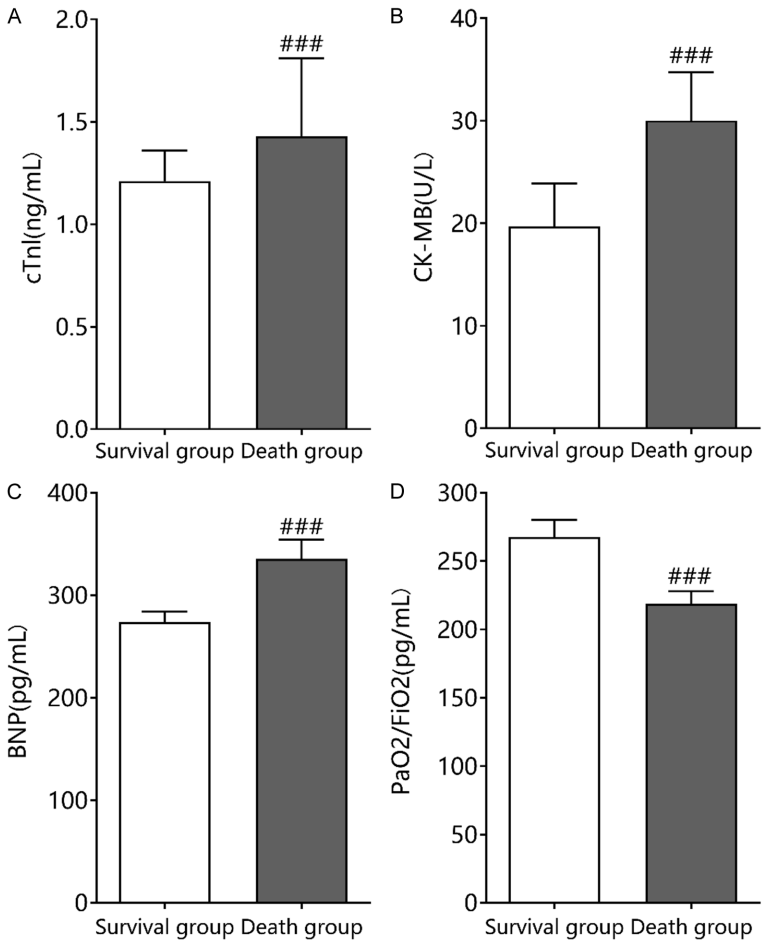

Figure 4. Comparison of myocardial injury indicators and oxygenation function indicators. A. cTnI; B. CK-MB; C. BNP; D. PaO_2/FiO_2. Compared with the survival group, ###P<0.001. cTnI, Cardiac troponin I; CK-MB, creatine kinase-MB; BNP, B-type natriuretic peptide; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen.

higher than those in the survival group (all P<0.05), indicating a more severe impairment of cardiac function. The oxygenation index (PaO_2/FiO_2) in the death group was markedly reduced (P<0.05), suggesting more severe pulmonary dysfunction and oxygenation impairment. See **Figure 4**.

Univariate logistic regression analysis of prognostic factors

The prognosis of children with ALL complicated by sepsis was defined as the dependent variable (survival = 0, death = 1), and univariate logistic regression analysis was performed with each candidate variable as the independent variable. The results indicated that leukemia remission status (PR/NR) within 48 hours after PICU admission, inflammatory response indicators (CRP, PCT, IL-6), and organ function indicators (ALT, AST, TBiL, Scr, BUN, cTnI, CK-MB, BNP) were significantly associated with mortality (all P< 0.05). Furthermore, 24-hour lactate clearance rate and PaO_2/FiO_2 ratio were inversely associated with mortality (both OR<1, P<0.05).

This study attempted to construct a multivariate Logistic regression model using the backward stepwise regression method. However, during the model fitting process, complete or quasi-complete separation was found between some independent variables and the outcome variables, which led to a significant increase in the standard errors of the model, unstable parameter estimation, and difficulty in obtaining regression results with statistical significance and clinical interpretability. Therefore, the results of the multivariate Logistic regression analysis were not further reported in this study. See **Table 6**.

Predictive value of PCIS, PEWS, and PSOFA scores for the prognosis

The prognosis of children (survival = 0, death = 1) was used as a state variable, and PCIS, PEWS, and PSOFA were used as test variables. The ROC curve results showed that the AUCs for the 3 scoring systems (PCIS, PEWS, and PSOFA) in predicting mortality in children with ALL complicated by sepsis were 0.751, 0.788, and 0.885, respectively. See **Tables 7**, **8** and **Figure 5**.

To compare the discriminatory abilities of the 3 scoring systems, the DeLong test was applied. The results showed that the AUC of the PSOFA score was significantly higher than those of the PEWS score (ΔAUC = 0.097, P = 0.005) and the PCIS score (ΔAUC = 0.134, P = 0.001); no statistically significant difference was found between the PEWS and PCIS scores (ΔAUC = 0.037, P = 0.415). See **Table 9**.

Table 6. Univariate logistic regression analysis of prognostic factors in children with ALL combined with sepsis

Variables	β	Standard Error	Wald χ^2	P	OR	95% CI
Leukemia remission status within 48 hours after PICU admission	1.178	0.283	17.348	0.000	3.249	1.866-5.656
24-hour lactate clearance rate	-0.0696	0.106	43.114	0.000	0.498	0.405-0.614
CRP	0.298	0.039	59.261	0.000	1.347	1.249-1.454
PCT	4.741	0.780	36.957	0.000	114.583	24.846-528.426
IL-6	0.237	0.046	26.602	0.000	1.267	1.158-1.386
ALT	0.483	0.108	20.091	0.000	1.621	1.312-2.002
AST	0.534	0.128	17.449	0.000	1.706	1.328-2.192
TBiL	1.162	0.172	45.800	0.000	3.196	2.283-4.474
Scr	0.177	0.033	28.336	0.000	1.193	1.118-1.273
BUN	2.159	0.314	47.211	0.000	8.664	4.680-16.041
cTnI	3.686	0.657	31.470	0.000	39.886	11.003-114.581
CK-MB	0.517	0.067	60.261	0.000	1.676	1.471-1.910
BNP	0.352	0.099	12.599	0.000	1.421	1.171-1.726
PaO_2/FiO_2	-0.318	0.070	20.866	0.000	0.728	0.635-0.834

Note: ALL, acute lymphoblastic leukemia; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBiL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; cTnI, cardiac troponin I; CK-MB, creatine kinase-MB; BNP, B-type natriuretic peptide; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen.

Table 7. Comparison of PCIS, PEWS and PSOFA scores

Prognosis	PCIS score	PEWS score	PSOFA score
Survival group (n=184)	75.27±5.26	4.11±0.76	10.21±1.87
Death group (n=76)	70.31±4.72	5.09±0.87	13.59±2.06
t	7.120	9.057	12.863
P	<0.001	<0.001	<0.001

Note: ALL, acute lymphoblastic leukemia; PCIS, Pediatric Critical Illness Score; PEWS, Paediatric Early Warning Score; PSOFA, Pediatric Sequential Organ Failure Assessment Score.

Discussion

This study systematically analyzed the infection characteristics and prognosis of children with ALL complicated with sepsis. Among these 260 children, 235 had a clear site of infection, mainly bloodstream infection, lung infection and multi-site infection, indicating that these children have wide infection range and the disease progresses rapidly. 132 cases were pathogen positive, mainly bacterial infection, which is consistent with the characteristic of opportunistic pathogens in the state of immunosuppression. In the clinical risk classification, ALL (HR) and ALL (IR) accounted for a high proportion (45.77% and 41.54%, respectively), indicating that children with IR and HR are more likely to develop serious infection in the early stage of treatment. After the 260 children were transferred to PICU, 184 survived (70.77%) and 76 died (29.23%), which was significantly lower than the PICU mortality rate (56.9%) reported by Wu et al. [18]. A retrospective study conducted by Singer et al. [19] at Mott Children's Hospital, University of Michigan, also showed that the mortality rate of children with acute leukemia complicated by sepsis (52%) was significantly higher than that of those without sepsis (17%). The difference in mortality across different studies may be related to factors such as children's age and the different medical conditions, but the results all suggest that sepsis is the main cause of death in the early treatment of ALL. Improving the survival rate of children with ALL complicated by sepsis who are transferred to the PICU is the key to improving the overall prognosis of children with ALL.

Univariate logistic regression analysis demonstrated that leukemia remission status (PR/NR) within 48 hours following PICU admission was significantly associated with mortality in these children. In addition, the proportion of children requiring invasive mechanical ventilation and inotropic support in the death group was higher than that in the survival group, although the difference was not statistically significant. These findings suggest that such supportive interventions primarily reflect disease severity rather than acting as independent prognostic factors. Our results are consistent with those reported by Wu et al. [20].

Table 8. Predictive value of PCIS, PEWS, and PSOFA scores for the prognosis of children with ALL combined with sepsis

Variables	Optimal cutoff value	AUC	Standard Error	P	95% CI
PCIS score	74.500	0.751	0.031	0.000	0.689-0.812
PEWS score	3.500	0.788	0.032	0.000	0.726-0.850
PSOFA score	11.500	0.885	0.022	0.000	0.841-0.929

Note: ALL, acute lymphoblastic leukemia; PCIS, Pediatric Critical Illness Score; PEWS, Paediatric Early Warning Score; pSOFA, Pediatric Sequential Organ Failure Assessment Score.

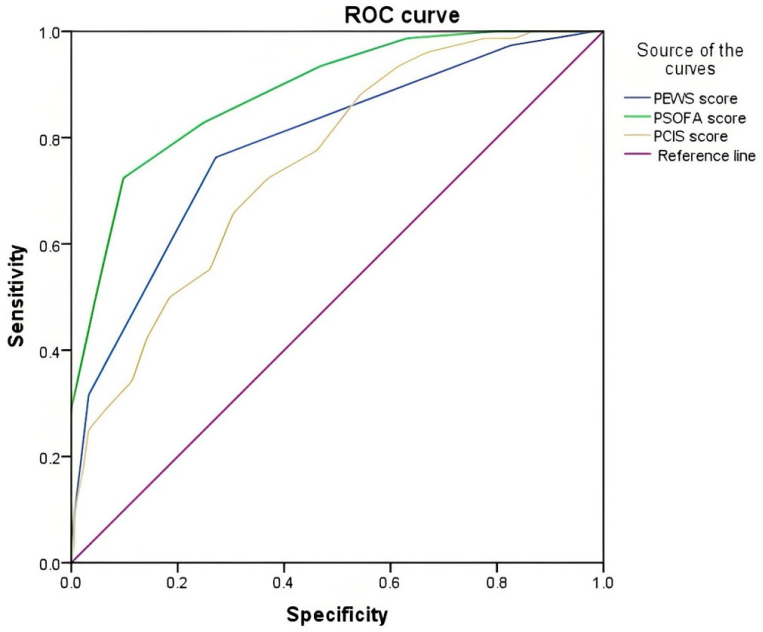

Figure 5. ROC curves of different scoring systems predicting mortality in children with ALL combined with sepsis. Note: ALL, acute lymphoblastic leukemia; PCIS, Pediatric Critical Illness Score; PEWS, Paediatric Early Warning Score; pSOFA, Pediatric Sequential Organ Failure Assessment Score.

The underlying mechanisms are as follows: (1) Leukemia remission status (PR/NR) with in 48 hours after PICU admission: In patients with PR/NR, residual leukemic cells in the bone marrow continuously suppress normal hematopoiesis, resulting in neutropenia and impaired phagocytic and bactericidal functions. Combined with chemotherapy-induced immunosuppression, the ability to clear pathogens is markedly compromised, predisposing patients to uncontrolled infection and rapid progression to severe sepsis or septic shock. Moreover, in unremitted leukemia, massive infiltration of the bone marrow by malignant lymphocytes replaces normal T and B lymphocytes, leading to impaired cellular and humoral immunity and an inability to mount an effective specific immune response against infectious pathogens.

(2) Invasive mechanical ventilation generally indicates severe respiratory dysfunction or respiratory failure and represents an important manifestation of disease severity. Although mechanical ventilation-related complications (e.g., ventilator-associated pneumonia, barotrauma) may exacerbate lung injury, the present study found no significant association between mechanical ventilation and mortality, indicating that it reflects the severity of the underlying disease rather than being a direct risk factor for death.

(3) The need for inotropic support suggests severe circulatory dysfunction, typically indicating progression to septic shock. This intervention reflects a state of hemodynamic decompensation rather than independently increasing mortality risk, which is supported by the non-significant association between inotropic support and mortality observed in this study.

With regard to inflammatory response, univariate logistic regression analysis revealed that elevated levels of CRP, PCT, IL-6 were significantly associated with mortality, while the 24-hour lactate clearance rate was negatively correlated with mortality.

The potential mechanisms underlying these associations may include the following: (1) Elevated levels of inflammatory factors such as CRP and PCT can trigger a cytokine storm, disrupt vascular endothelial integrity, and increase vascular permeability. Fluid and pro-

Table 9. Comparison of AUCs among the three scoring systems using the Delong test

Comparison Groups	*z*-value	*p*-value	AUC Difference	Standard Error	95% Confidence Interval
PEWS score vs PSOFA score	-2.815	0.005	-0.097	0.034	(-0.164, -0.029)
PEWS score vs PCIS score	0.816	0.415	0.037	0.045	(-0.052, 0.127)
PSOFA score vs PCIS score	3.33	0.001	0.134	0.04	(0.055, 0.213)

tein leak from the vasculature into the interstitial space, leading to serious complications such as acute respiratory distress syndrome, severe systemic edema, and a sudden decrease in effective circulating blood volume, which may accelerate disease progression to septic shock [21]. Additionally, an excessive inflammatory response can inhibit the anticoagulation and fibrinolytic system, promote microthrombus formation, and aggravate tissue ischemia and hypoxia. (2) Lactate is the end product of anaerobic glycolysis. Under normal conditions, most pyruvate enters the mitochondria for complete oxidation; only a small fraction is converted to lactate. A decreased 24-hour lactate clearance rate reflects severe infection with excessive production of inflammatory mediators and cytokines, leading to microcirculatory disturbances, blood stasis, and decreased capillary density. These changes impair oxygen delivery to tissues, thereby suppressing aerobic glucose metabolism and promoting anaerobic glycolysis. Furthermore, a decreased 24-hour lactate clearance rate suggests that initial resuscitation measures (e.g., fluid resuscitation and vasoactive agents) have failed to reverse tissue hypoperfusion. Persistent hypoperfusion can further compromise myocardial contractility, precipitate heart failure, and ultimately drive the progression of multiple organ dysfunction syndrome.

Additionally, univariate logistic regression analysis also demonstrated that organ function indicators (ALT, AST, TBiL, Scr, BUN, cTnI, CK-MB, BNP) were significantly associated with mortality. The PaO_2/FiO_2 ratio was inversely associated with mortality. The mechanisms are as follows: (1) A decreased PaO_2/FiO_2 ratio indicates severe impairment in pulmonary gas exchange, which fails to meet systemic oxygen demand. Sustained hypoxia in oxygen-dependent organs (heart, brain, kidneys) leads to reduced myocardial contractility, cerebral dysfunction, and renal tubular injury, directly inducing cardiac insufficiency, impaired consciousness, and acute kidney injury. In children with ALL and sepsis, the inflammatory response frequently causes alveolar exudation and interstitial edema. Exudative fluid and inflammatory cells inactivate pulmonary surfactant and fill alveolar spaces, leading to diffuse alveolar collapse, reduced lung compliance, and even acute respiratory distress syndrome, which further impairs oxygenation and accelerates clinical deterioration [22].

(2) Elevated ALT and AST indicate hepatocellular injury, while increased TBiL reflects cholestasis or impaired hepatic uptake and excretion. Chemotherapeutic agents are intrinsically hepatotoxic, and liver dysfunction results in rapid deterioration of metabolic, detoxification, and synthetic functions, which may render the body unable to effectively metabolize drugs or clear toxins, which may even lead to circulatory failure. Increased Scr and BUN indicate reduced glomerular filtration or renal tubular injury. As a key organ for maintaining homeostasis, renal dysfunction impairs the clearance of metabolic acids, excess water, and disrupts electrolyte balance (e.g., potassium and sodium), electrolytes, potentially causing severe acidosis, fatal hyperkalemia, and fluid overload, which may precipitate acute heart failure and increase mortality risk. Elevated cTnI and CK-MB indicate myocardial necrosis, and increased BNP suggests ventricular overload or cardiac dysfunction. Reduced cardiac output further exacerbates tissue hypoperfusion, creating a vicious cycle and significantly increasing mortality risk.

ROC curve analysis showed that the AUCs of the PCIS, PEWS, and PSOFA scores for predicting mortality in children with ALL complicated by sepsis were 0.751, 0.788 and 0.885, respectively. The PSOFA score exhibited the highest predictive performance, followed by the PEWS and PCIS scores, which is consistent with the findings of Liu et al. [23]. These results suggest that multi-dimensional scoring systems can facilitate the early identification of high-risk patients, guide PICU treatment strate-

gies, and optimize the timing of interventions to improve prognosis.

This study still has several limitations. First, as a single-center retrospective study with a relatively small sample size, selection bias may exist, and the generalizability of the conclusions should be interpreted with caution. Second, some laboratory and clinical parameters were only measured in the early phase after PICU admission without dynamic monitoring, which may not fully reflect their temporal changes during disease progression and may affect the accuracy of prognostic evaluation.

In addition, although univariate logistic regression was used to systematically evaluate potential prognostic factors, the limited number of events and the presence of complete or quasi-complete separation between some variables and the outcome prevented the construction of a stable multivariate model. Thus, independent prognostic factors could not be identified, and residual confounding may remain.

Finally, PICU management strategies vary across institutions. Further multi-center, large-sample, prospective studies are warranted to validate the identified risk factors and enhance the robustness and clinical applicability of the findings.

Conclusions

Children with ALL complicated by sepsis commonly present with bloodstream infection, pulmonary infection, multi-site infection, bacterial infection, and IR/HR stratification, and carry a high mortality risk following PICU admission.

Leukemia remission status within 48 hours after PICU admission, decreased 24-hour lactate clearance rate, excessive inflammatory response, and impaired multi-organ and respiratory function are all associated with poor prognosis.

The PSOFA score demonstrates superior predictive performance for mortality compared with the PEWS and PCIS scores. The combination of multi-dimensional clinical indicators and scoring systems facilitates early risk stratification and helps guide PICU treatment decisions.

Disclosure of conflict of interest

None.

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