

Original article

Prognostic factors and outcomes of pediatric acute lymphoblastic leukemia using ThaiPOG protocols: a single institute experience

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Abstract:

Background: Acute lymphoblastic leukemia (ALL) is the most common malignancy among children. Disease-based risk stratification was incorporated in the Thai Pediatric Oncology Group (ThaiPOG) protocols to adjust intensive chemotherapies, and central nervous system-directed treatment. Although treatment outcomes have improved over the decade, excellent outcomes are counterbalanced by treatment-related toxicities, especially in countries with limited resources like Thailand. **Objective:** The single institute study aimed to evaluate prognostic factors associated with survival outcomes in pediatric ALL using ThaiPOG protocols at Phramongkutklo Hospital. **Materials and methods:** Pediatric patients with ALL treated at Phramongkutklo Hospital between 2014 and 2019 were retrospectively reviewed. **Results:** In total, 50 patients with a median age of 9.64 (range, 0.34-19.81) years were studied. The most common immunophenotype was pre-B cell ALL (N = 42, 84%). The 5-year overall survival (OS) and event-free survival (EFS) were 80% and 76%, respectively. The major mortality cause was treatment-related infection (N = 7, 14%). Unfavorable cytogenetics was the only factor associated with OS ($p = 0.006$) and EFS ($p < 0.001$). **Conclusion:** The outcomes of pediatric ALL in Thailand were comparable to those of developed countries. Cytogenetic testing is essential for stratifying disease status and tailoring treatment protocol accordingly. Infections remain the leading cause of death among pediatric patients with ALL.

Keywords : ● Pediatric acute lymphoblastic leukemia ● Survival ● Cytogenetics ● Infection

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นิพนธ์ต้นฉบับ

ปัจจัยการพยากรณ์โรคและผลลัพธ์ของโรคมะเร็งเม็ดเลือดขาวเฉียบพลันในเด็ก โดยใช้แนวทางการรักษาของชมรมโรคมะเร็งเด็กแห่งประเทศไทย: ประสิทธิภาพของโรงพยาบาลพระมงกุฎเกล้า

นวัชชัย เลิศวิวัฒน์พงษ์ พิยะ รุจกิจยานนท์ ชาญชัย ไตรวารี และ ชาลินี มนต์เสริญสุรณี
สาขาวิชาโลหิตวิทยาและมะเร็งในเด็ก ภาควิชากุมารเวชศาสตร์ โรงพยาบาลพระมงกุฎเกล้า และวิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า

บทคัดย่อ

ที่มาและความสำคัญ มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบลาสติก (*acute lymphoblastic leukemia, ALL*) เป็นโรคมะเร็งที่พบบ่อยที่สุดในเด็ก การแบ่งกลุ่มเสี่ยงของโรคนั้นได้กำหนดไว้ตามแนวทางการรักษาของชมรมโรคมะเร็งในเด็กแห่งประเทศไทย (ThaiPOG) เพื่อใช้ปรับเคมีบำบัดให้มีความเข้มข้นขึ้นตามความเสี่ยงของโรค และป้องกันหรือรักษาตัวโรคที่แพร่กระจายเข้าสู่ระบบประสาทส่วนกลาง แม้ว่าผลลัพธ์ของการรักษาจะดีขึ้นในช่วงทศวรรษที่ผ่านมา แต่ผู้ป่วยอาจต้องพบกับความเสี่ยงด้านผลข้างเคียงจากการรักษา โดยเฉพาะอย่างยิ่งในประเทศที่มีทรัพยากรจำกัด เช่น ประเทศไทย **วัตถุประสงค์** การศึกษาวิจัยในสถาบันเดียวนี้ เพื่อประเมินปัจจัยการพยากรณ์โรคที่เกี่ยวข้องกับอัตราการรอดชีวิตในผู้ป่วย ALL ด้วยแนวทางการรักษาของ ThaiPOG ในโรงพยาบาลพระมงกุฎเกล้า **แนวทางและวิธีการ** ผู้ป่วยเด็กที่เป็น ALL ที่ได้รับการรักษาที่โรงพยาบาลพระมงกุฎเกล้าระหว่างปี 2014 ถึง 2019 ได้รับการทบทวนเวชระเบียนย้อนหลัง **ผลลัพธ์** จากการศึกษาผู้ป่วยทั้งหมด 50 รายที่มีอายุเฉลี่ย 9.64 ปี (ช่วง 0.34-19.81 ปี) ชนิดของอิมมูโนโอฟิโนไทป์ที่พบบ่อยที่สุดคือ pre-B cell ALL (n = 42, 84%) อัตราการรอดชีวิตโดยรวม (OS) และ อัตราการรอดชีวิตโดยปราศจากโรค (EFS) อยู่ที่ร้อยละ 80 และ 76 ตามลำดับ สาเหตุการเสียชีวิตหลักคือการติดเชื้อที่เกี่ยวข้องกับการรักษา (n = 7, 14%) และผลตรวจโครโมโซมที่ไม่พึงประสงค์เป็นปัจจัยเดียวที่เกี่ยวข้องกับ OS (p = 0.006) และ EFS (p < 0.001) **สรุป** ผลการรักษา ALL ในเด็กด้วยการใช้แนวทางการรักษาในประเทศไทยเทียบได้กับประเทศพัฒนาแล้ว แต่ยังคงมีความจำเป็นต้องมีการตรวจโครโมโซม เพื่อแบ่งกลุ่มความเสี่ยงของโรคและกำหนดแนวทางการรักษา ในขณะที่การติดเชื้อยังคงเป็นสาเหตุหลักของการเสียชีวิตในผู้ป่วยเด็กที่เป็น ALL

คำสำคัญ : ● มะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมโฟบลาสติกในเด็ก ● อัตราการรอดชีวิต ● ไซโตเจเนติกส์ ● การติดเชื้อ
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Introduction

Leukemia is the most common malignancy among pediatric patients worldwide.^{1,2} The most common subtype of leukemia is acute lymphoblastic leukemia (ALL), accounting for more than 70%, followed by acute myeloid leukemia and chronic myeloid leukemia, respectively.²⁻⁴

The standard treatment for pediatric ALL consists of multiagent systemic chemotherapies. Treatment intensities are stratified based on risk groups according to the risk-adapted therapy strategy, which relies on clinical and diagnostic criteria.^{5,6} Prognostic factors include age at diagnosis, initial white blood cell (WBC) count, central nervous system (CNS) and testicular involvement, immunophenotypes, cytogenetic abnormalities, steroid pretreatment, minimal residual disease (MRD) evaluation, and other specified conditions such as constitutional trisomy 21.⁶ However, some laboratory diagnostics are inaccessible in many institutions across Thailand, affecting treatment plans and subsequently reflecting on outcomes.

Although treatment outcomes in pediatric ALL have improved over time,⁷ treatment-related toxicity or infectious complications are still common. Infection remains the most common cause of death in pediatric ALL, especially in countries with limited resources,⁸ requiring prompt and appropriate supportive and symptomatic care.

The Thai Pediatric Oncology Group (ThaiPOG) is a national organization in Thailand dedicated exclusively to the treatment of childhood and adolescent cancers. ThaiPOG treatment protocols for ALL, named ThaiPOG-ALL, were first established in the mid-2010s. These protocols were adapted from standard Children Oncology Group study protocols and have been used as national protocols for treating pediatric ALL patients in Thailand since 2013.

This study aims to describe the clinical characteristics, prognostic factors, and outcomes in pediatric ALL using ThaiPOG protocols in a single institution. The results should provide a better comprehension of the status of ALL, which may reflect the overall situation of ALL in Thailand.

Materials and methods

Patient selection

The medical records of 50 newly diagnosed pediatric patients with ALL were retrospectively reviewed. The patients were treated primarily at the Department of Pediatrics, Phramongkutklo Hospital, between January 1, 2014, and December 31, 2019.

The study's inclusion criteria included patients with newly diagnosed ALL aged < 18 years. Patients with uncertain diagnoses, incomplete medical records, those who refused or abandoned treatment, and those who were lost to follow-up were excluded from the study.

Written informed consent and assent were waived. This study was approved by the Ethics Committee and Institutional Review Board of Phramongkutklo Hospital and Phramongkutklo College of Medicine, Bangkok, Thailand, in accordance with the ethics principles of the Declaration of Helsinki (1975) and its revision (reference number: IRBRTA1013/2567).

Clinical definitions

The cytogenetic technique used was conventional chromosome karyotyping, while the molecular technique was multiplex RT-PCR for *BCR/ABL* p190, *TEL/AML1*, *E2A-PBX1*, and *MLL-AF4*. At our institute, we strive to perform both cytogenetic and molecular investigations among patients with ALL. However, financial constraints remain a significant obstacle in resource-limited countries.

CNS involvement was classified into three categories; CNS-1 was defined as the absence of blasts, CNS-2 as < 5 WBCs/mm³ with blasts or traumatic LP; and CNS-3 as ≥ 5 WBCs/mm³ with blasts or any facial nerves palsy, or brain and eye involvement.

Steroid pretreatment was defined as the administration of systemic corticosteroids for more than 24 hours at any time within two weeks before diagnosis.

Treatment protocols

Since 2013, Thai children with ALL have been risk-stratified as standard, high, extremely high, Philadelphia chromosome-positive, and infantile subgroup according to the ThaiPOG National Protocol for ALL and

treated accordingly under the ThaiPOG-ALL-1301 to 1307 protocols, respectively (excluding ThaiPOG-ALL-1305, which constitutes the relapsed ALL protocol).

The ThaiPOG ALL protocol comprises a risk-stratified therapy, classified based on clinical and molecular criteria. Clinical criteria include immunophenotyping, age groups, organ involvement (CNS and testicular), steroid pretreatment, induction failure, and Down syndrome. Molecular criteria include MRD status, favorable/unfavorable cytogenetics, and other unfavorable molecular features.

Results

Patient demographic data

A total of 50 patients with childhood ALL were enrolled in this study. Patient characteristics including age, sex, disease involvement, initial WBC count, CNS status, immunophenotype, molecular features, bone marrow status after induction, and treatment stratification are shown in Table 1.

The median age at diagnosis was 9.64 (range, 0.34-19.81) years. The most common age group was 1 to 9.99 years ($n = 32$, 64%). The male-to-female ratio was 1:0.85. Extramedullary manifestations included CNS involvement ($n = 8$, 16%) and mediastinal mass ($n = 4$, 8%). The initial WBC count at diagnosis was $\geq 50,000/\text{mm}^3$ in 30% of patients ($n = 15$). One patient ($n = 2\%$) received steroid pretreatment.

The most common immunophenotype was pre-B cell ALL ($n = 42$, 84%). Cytogenetic studies were performed in 80% ($n = 40$) of the patients due to the financial limitation. Cytogenetic abnormalities were identified in 15 (37.5%) of the 40 patients who underwent testing. Favorable molecular features ($n = 3$, 7.5%) included hyperdiploid ($n = 2$, 5%) and $t(12;21)$ or *ETV6/RUNX1*, *TEL/AML1* ($n = 1$, 2.5%). Unfavorable molecular features ($n = 4$, 10%) included hypodiploid ($n = 1$, 2.5%), Philadelphia chromosome $t(9;22)$ ($n = 2$, 5%), and 11q23 or *KMT2A* ($n = 1$, 2.5%). The *KMT2A* rearrangement was found in one infant with ALL, while the other infant

Table 1 Patient characteristics with acute lymphoblastic leukemia

	n	%
Age at diagnosis (years)		
Median (range)	9.64 (0.34-19.81)	
Age group (years)		
Less than 1	2	4.0
1-9.99	32	64.0
10-13.99	12	24.0
14 or above	4	8.0
Immunophenotype		
Pre-B-cell	42	84.0
T-cell	8	16.0
Mixed	0	0.0
CNS involvement*		
CNS 1	42	84.0
CNS 2	5	10.0
CNS 3	3	6.0
Mediastinal mass		
No	46	92.0
Yes	4	8.0
Testicular involvement		
No	27	100.0
Yes	0	0.0
Steroid pretreatment		
No	49	98.0
Yes	1	2.0
WBC count (cell/mm ³)		
Less than 50,000	35	70.0
50,000 and above	15	30.0
Cytogenetic investigation		
Done	40	80.0
Not done	10	20.0
Molecular investigation		
Done	20	40.0
Not done	30	60.0
Bone marrow status at day 29		
M1	46	92.0
M2	0	0.0
M3	0	0.0
Not done	4	8

Table 1 Patient characteristics with acute lymphoblastic leukemia (continue)

	n	%
MRD status at day 29		
Negative	43	93.5
Positive	3	6.5
Risk stratification and postinduction outcome		
Standard	18	36.0
High risk	18	36.0
Very high risk	11	22.0
Infantile ALL	2	4.0
Death	1	2.0
Treatment protocol		
ThaiPOG-ALL-1301	12	24.0
ThaiPOG-ALL-1302	21	42.0
ThaiPOG-ALL-1303	8	16.0
ThaiPOG-ALL-1304	2	4.0
Other	7	14.0

had normal cytogenetic. Other cytogenetic findings (n = 3, 7.5%) included t(1;19) (n = 1, 2.5%), t(4;11) (n = 1, 2.5%) and t(9;11) (n = 1, 2.5%).

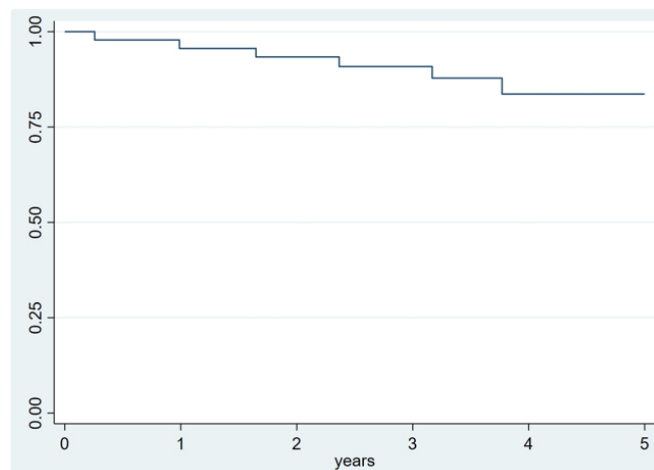
Most patients with ALL (n = 43, 86%) were treated following the ThaiPOG-ALL protocols. Twelve patients (24.0%) were classified as presenting standard risk, and 21 patients (42.0%) were classified as high risk. Eight patients (16.0%) were classified as very high risk, while two patients (4.0%) were classified as Philadelphia chromosome-positive. Two patients (4.0%) were classified

as infantile risk. The remaining patients (n = 5, 10.2%) received total therapy (total XV and total XVI) treatment protocols, adapted from St. Jude Children's Hospital, TN, USA, based on institutional experts' experiences.

Outcomes

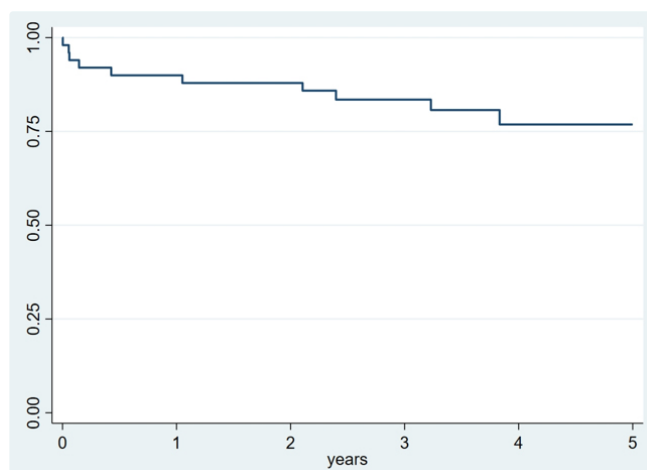
At the end of the study, 10 (20%) patients died. Of these, 2 (20%) died from disease relapse, and 8 (80%) died from therapy-related infections. The relapsed patients comprised a standard-risk patient and a very high risk patient.

Unfortunately, one patient with high risk ALL died during the induction phase due to disseminated fungal infection and septic shock. Regarding postinduction outcome, MRD (identified by flow cytometry) was positive in three patients (6.5%). The MRD-positive patients included two in the high risk group and one in the very high risk group. Cytogenetic or molecular abnormalities resulted in major changes to risk stratification criteria. Disease relapse occurred in two patients (20%). Among these relapsed patients, one was a standard-risk patient undergoing treatment in the maintenance phase during cycle 7, week 1, and was classified as having an isolated CNS relapse. The other patient was a very high-risk patient who experienced a very early combined relapse before starting the maintenance phase treatment. The OS (Figure 1) and EFS (Figure 2) of pediatric patients with ALL are demonstrated. Five-year OS and EFS were 80% (95%CI: 74%-96%) and 76% (95%CI: 68%-87%), respectively.



Note: Survival outcomes were calculated using the Kaplan-Meier method.

Figure 1. Overall survival among patients with childhood acute lymphoblastic leukemia (n = 50)



Note: Survival outcomes were calculated using the Kaplan-Meier method.

Figure 2 Event-free survival among patients with childhood acute lymphoblastic leukemia (n = 50)

Multivariate analysis of factors associated with outcomes in childhood ALL

After adjusting for age at diagnosis, risk stratification, steroid pretreatment, and extramedullary involvements, OS and EFS were significantly associated with unfavorable cytogenetics with statistical significance (HR = 10.422, $p = 0.006$ and HR = 12.831, $p < 0.001$, respectively).

Discussion

Acute lymphoblastic leukemia is the most common malignancy among the children.¹⁻⁴ The outcomes of the disease and treatment have improved over the decades, especially in developing or lower-middle income countries (LMIC).^{3-5,9} In Thailand, the drive to improve outcomes led to the establishment of the National Child Cancer Society (Thai pediatric oncology group - ThaiPOG) to develop and reach the consensus on the national treatment protocol in 2014. The national pediatric ALL protocol was adapted from standard protocols used in developed countries, such as Children Oncology Group protocol in the US. By implementing risk stratification criteria, multi-agent chemotherapy, and CNS prophylaxis via direct intrathecal therapy, treatment outcomes improved significantly.⁸ Consequently, the survival rate has improved substantially over the years.

Among patients with ALL, multiple prognostic factors--including the patients' age at diagnosis, initial white blood cell count, steroid pretreatment, immunophenotype

of leukemic cells, and cytogenetic abnormalities--were respectively analyzed. In this study, the most common age group in pediatric ALL was 1 to 9.99 years old and immunophenotype Pre-B cell ALL (more than 80%) was more common than T-cell ALL (less than 20%). The findings align closely with data from the EU and US.^{6,7} This age group and immunophenotype remain the most common presentation of ALL.^{3,4,8,9}

The most common extramedullary manifestation was CNS involvement, which is the most frequently affected sanctuary site.⁷ Thus, lumbar puncture for CSF analysis with cyto centrifugation is recommended for every patient with ALL, except in cases where contraindications exist, such as focal neurologic deficits or bleeding tendencies.¹⁰

Conventional karyotyping or molecular genetic testing is crucial and often prioritized over patient history or basic laboratory criteria, because it is essential for refining risk stratification.⁸ Pediatric oncology treatment centers are increasingly equipped to perform these investigations. This study demonstrated that, beyond refining risk criteria, these tools influence OS and EFS, which will be discussed further. Moreover, bone marrow MRD investigation on Day 29 is recommended for these patients.¹¹

The induction-phase mortality rate was 2%, primarily due to uncontrolled infection complications. Infections remain a significant challenge, especially in LMIC. Early

Table 2 Multivariable analysis of risk factors associated with outcomes in childhood acute lymphoblastic leukemia (n = 50)

	Overall survival (OS)			Event-free survival (EFS)		
	Hazard ratio	p-value	95%CI	Hazard ratio	p-value	95%CI
Age group (years)						
≤ 1	2.617	0.500	0.160-42.732	4.589	0.490	0.301-50.378
1-9	1			1		
10-13	0.621	0.698	0.056-6.900	1.032	0.513	0.170-7.932
≥ 14	1.698	0.241	0.483-5.583	1.761	0.216	0.563-6.794
Sex						
Male	1.340	0.651	0.378-4.752	1.632	0.881	0.482-5.172
Female	1			1		
Immunophenotype						
T-cell	3.140	0.100	0.805-12.251	4.537	0.092	0.914-14.782
Pre-B cell	1			1		
Initial WBC count (/mm ³)						
≥ 50,000	2.759	0.109	0.797-9.554	3.184	0.089	0.871-10.643
< 50,000	1			1		
Cytogenetic test						
Unfavorable	10.422	0.006*	1.964-55.299	12.831	<0.001*	2.635-70.984
Favorable	1			1		
MRD status Day 29 of induction						
≥ 0.01%	3.887	0.217	0.451-33.511	5.120	0.131	0.572-43.834
< 0.01%	1			1		
Protocol of treatment						
ThaiPOG-ALL-1301	1			1		
ThaiPOG-ALL-1302	1.004	0.997	0.167-6.018	1.002	0.996	0.178-5.648
ThaiPOG-ALL-1303	1.631	0.625	0.229-11.622	1.723	0.613	0.245-11.344
ThaiPOG-ALL-1304	1.869	0.494	0.311-11.244	1.992	0.437	0.362-10.982
Other	1.787	0.329	0.212-12.452	1.831	0.311	0.201-13.826

Notes: Univariate analysis was calculated using Cox's Proportion Hazard Model. *P*-value < 0.05 was considered statistical significance. Unfavorable cytogenetic abnormalities included hypodiploidy, t(1,19), and 11q23 (*KMT2A*). Hypodiploid was defined when a chromosome count < 44 chromosomes or DNA index < 0.81. **Abbreviations:** CI, confidence interval; MRD, minimal residual disease; WBC, white blood cell

detection, evaluation, close observation, and empirical antibiotics are crucial for patients with ALL and febrile neutropenia. Patients with prolonged febrile neutropenia are particularly susceptible to fungal infections, empirical antifungal agents should be considered at the initial stage.¹²

A total of 15 patients with ALL (27.5%) in this study presented with cytogenetic abnormalities, a finding comparable to related studies.^{13,14} Hypodiploidy, t(1,19), and 11q23 (*KMT2A*)--considered unfavorable cytogenetic abnormalities--were found in three patients (7.5%). This study excluded t(9,22) because targeted therapy with-

imatinib mesylate, launched in 2001 and incorporated into the Children's Oncology Group protocol (AALL0031) has improved OS and EFS in pediatric ALL.¹⁵ Thus, t(9,22) was not considered an unfavorable cytogenetic abnormality in this context. Moreover, t(1,19) was classified as a high-risk cytogenetic abnormality due to its association with a higher risk for CNS involvement and relapse.¹⁶

The five-year OS for pediatric ALL treated at Phramongkutklao Hospital between 2014 and 2019 was 80%, and the five-year EFS was 76%. Compared with the related study,⁹ OS and EFS have improved over the years. This improvement may be attributed to the implementation of the national protocol, advancement in the multidisciplinary care team, and close follow-up of patients.

The end-of-treatment follow-up among pediatric patients with ALL showed that ten patients had died. The major cause of death among seven patients (14%) was bacterial and fungal infections. One hypodiploid, high risk patient was lost during the induction phase; one t(1;19), high-risk patient was lost during the augmented-consolidation phase; one normal cytogenetic, very high risk patient was lost during the augmented-interim-maintenance phase; and one KMT2A infant was lost during continuation phase IV. Additionally, two normal cytogenetic, standard-risk patients were lost during the maintenance phase. The remaining patients were lost within six months after maintenance due to CMV and cryptococcal infections. Clearly, infections remain the main cause of death among oncologic patients.^{8,9,12} Therefore, comprehensive, supportive, and multidisciplinary care teams are required to care for patients with cancer. Disease-related mortality was found among two patients (20% of all mortality) and was associated with disease relapse or refractory status.

Multivariate analysis in Cox's proportional hazards model revealed associated factors associated with OS and EFS in pediatric ALL at Phramongkutklao Hospital, adjusted with age at diagnosis, risk stratification,

steroid pretreatment, and extramedullary involvements. OS showed a statistically significant association with unfavorable cytogenetics (HR = 10.422, $p = 0.006$); consequently, the association with EFS was also statistically significant (HR = 12.831, $p < 0.001$). As previously mentioned, cytogenetic or molecular abnormalities were more predictive than historical or basic laboratory criteria because survival outcomes were statistically significant.^{13,14} Even though a related study in Thailand did not show any significant association with cytogenetics,⁹ this investigation, conducted among patients with ALL (80%), was sufficient to distinguish differences in treatment outcomes. Therefore, pediatric patients with ALL and high risk cytogenetic abnormalities might benefit from more intense multiagent chemotherapies, longer treatment duration, and/or closed monitoring for disease relapse.⁸

Moreover, other prognostic factors did not show any significant association. Age group, T-cell immunophenotype, and initial WBC count showed no statistical significance. Regarding age, a previous study showed that age is a critical prognostic factor in pediatric ALL, with children aged one to nine years experiencing better outcomes compared to infants (< 1 year) and adolescents (≥ 10 years).¹⁸ Historically, T-cell ALL has been associated with poorer outcomes compared with B-cell ALL due to higher relapse rates and resistance to therapy. However, recent studies have demonstrated significant improvements in survival rates for T-cell ALL with contemporary protocols (e.g., Children's Oncology Group trials).¹⁹ A high initial WBC count ($> 50,000/\mu\text{L}$) is typically associated with poorer prognosis in pediatric ALL.¹⁸ In this study, other factors, such as MRD or cytogenetics, may have played a more dominant role in determining outcomes. Furthermore, these results might have stemmed from the well-organized disease-based risk-stratification regimen,⁶ resulting in uniform distribution of risk groups and effective treatment protocols that minimized the impact of these factors. Moreover, MRD, which has been identified as

the most potent prognostic factor in pediatric ALL in related studies, was not associated with the disease outcome in this study.^{17,18} The reason may lie in close postinduction monitoring. MRD after the end of the induction phase (EOI) is itself a measure of disease response and treatment outcome. Following positive MRD results after EOI, risk stratification was upscaled to high- or very-high-risk regimen and reevaluated after the end of the consolidation phase (EOC).¹⁹ In this study, only one patient indicated positive MRD after both EOI and EOC and was considered to have refractory disease. This patient was unable to receive hematopoietic stem cell transplantation and passed away from the disease.

Limitations

While the study covered a period of four years, the relatively small sample size (50 patients) from single center may limit the generalizability of the findings. Despite this, our findings provide valuable insights into the outcomes and challenges faced in treating ALL within a pediatric population. Future studies with larger cohorts and multi-center collaborations should be conducted to explore, validate, and expand real situation in pediatric ALL in Thailand. Moreover, this study was a retrospective investigation in which some data were unavailable.

Conclusion

Improvement in outcomes for pediatric ALL was addressed in this study. It was advised that conventional karyotyping analyses are necessary to stratify disease status and designate treatment protocols accordingly. Infections remained the main cause of death among pediatric patients with ALL. Therefore, comprehensive, supportive, and multidisciplinary care teams are required for early detection, evaluation, and early prompt treatment of ALL patients with infectious complications.

Declarations

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Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy or ethical restriction. The data are available from the corresponding author upon reasonable request.

Authors' contributions

NL interpreted data, drafted and edited the manuscript. CM conceptualized and designed the study, accumulated, analyzed and interpreted data and managed the program overall. PR and CT participated in study design, data collection, statistical analysis and manuscript writing. All the authors participated in draft revisions and approved of the final manuscript.

References

1. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol.* 2017;18:719-31.
2. World Health Organization. (2021). CureAll framework: WHO global initiative for childhood cancer: increasing access, advancing quality, saving lives. World Health Organization. <https://www.who.int/publications/i/item/9789240025271>.
3. Wiangnon S, Kamsa-Ard S, Jetsrisuparb A, Sriplung H, Sontipong S, Sumitsawan Y, et al. Childhood cancer in Thailand: 1995-1997. *Asian Pac J Cancer Prev.* 2003;4:337-43.
4. Wiangnon S, Veerakul G, Nuchprayoon I, Seksarn P, Hongeng S, Krutvecho T, et al. Childhood cancer incidence and survival 2003-2005, Thailand: study from the Thai Pediatric Oncology Group. *Asian Pac J Cancer Prev.* 2011;12:2215-20.
5. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med.* 2009;360:2730-41.
6. Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). *Blood.* 2007;109:926-35.

7. Gatta G, Rossi S, Foschi R, Trama A, Marcos-Gragera R, Pastore G, et al. Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002. *Haematologica*. 2013;98:744-52.
8. Choudhry VP, Krishnamurthy L, Arya LS, Desai N, Pati H. Causes of mortality in children with acute lymphocytic leukemia. *Indian Pediatr*. 1992;29:709-13.
9. Rujkijyanont P, Kaewinsang S, Monsereenusorn C, Traivaree C. Pediatric Acute Leukemia: The Effect of Prognostic Factors on Clinical Outcomes at Phramongkutklao Hospital, Bangkok, Thailand. *J Med Assoc Thai*. 2014;97(Suppl. 2):S188-95.
10. Schulga P, Grattan R, Napier C, Babiker MO. How to use... lumbar puncture in children. *Arch Dis Child Educ Pract Ed*. 2015;100:264-71.
11. Kruse A, Abdel-Azim N, Kim HN, Ruan Y, Phan V, Ogana H, et al. Minimal Residual Disease Detection in Acute Lymphoblastic Leukemia. *Int J Mol Sci*. 2020;21:1054.
12. Monsereenusorn C, Sricharoen T, Rujkijyanont P, Suwanpakdee D, Photia A, Lertvivatpong N, et al. Clinical Characteristics and Predictive Factors of Invasive Fungal Disease in Pediatric Oncology Patients with Febrile Neutropenia in a Country with Limited Resources. *Pediatric Health Med Ther*. 2021;12:335-45.
13. Crist WM, Pui CH. Clinical implications of cytogenetic and molecular analyses of pediatric acute lymphoblastic leukemia. *Stem Cells*. 1993;11:81-7.
14. Chennamaneni R, Gundeti S, Konatam ML, Bala S, Kumar A, Srinivas L. Impact of cytogenetics on outcomes in pediatric acute lymphoblastic leukemia. *South Asian J Cancer*. 2018;7:263-6.
15. Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol*. 2009;27:5175-81.
16. Jeha S, Pei D, Raimondi SC, Onciu M, Campana D, Cheng C, et al. Increased risk for CNS relapse in pre-B cell leukemia with the t(1;19)/TCF3-PBX1. *Leukemia*. 2009;23:1406-9.
17. Health Quality Ontario. Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia: A Clinical Evidence Review. *Ont Health Technol Assess Ser*. 2016;16:1-52.
18. Mörücke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2,169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood*. 2008;111(9):4477-89.
19. Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111(12):5477-85.