นิพนธ์ต้นฉบับ

อัตราการรอดชีพของผู้ป่วยมะเร็งเม็ดเลือดขาวเฉียบพลันชนิดลิมฟอยด์ที่มีภาวะเม็ดเลือดขาวสูงมากผิดปกติ (hyperleukocytosis) ในผู้ป่วยเด็ก โรงพยาบาลอุดรธานี

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กลุ่มงานกุมารเวชกรรม โรงพยาบาลอุดรธานี

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บทคัดย่อ

ความเป็นมา: โรคมะเร็งเม็ดเลือดขาวเป็นโรคมะเร็งในเด็กที่พบบ่อยที่สุด ผู้ป่วยส่วนใหญ่มีโอกาสหายขาดสูงจากการรักษามาตรฐาน แต่อย่างไรก็ตามผู้ป่วยที่มีเม็ดเลือดขาวสูง (hyperleukocytosis) อาจจะไม่แสดงอาการหรือมีอาการผิดปกติเช่น ซึม ปัสสาวะออกน้อย เป็นต้น การมีภาวะเม็ดเลือดขาวสูงจะเพิ่มความเสี่ยงต่อภาวะแทรกซ้อนและการเสียชีวิตในระยะแรก จากข้อมูลการศึกษาในประเทศที่พัฒนาแล้วพบว่าโอกาสหายขาดจากมะเร็งเม็ดเลือดขาวที่มีอาการเม็ดเลือดขาวสูง ในผู้ป่วยเด็กชนิด acute lymphoblastic leukemia คิดเป็นร้อยละ 64.5 จากการศึกษาของคณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ พบว่าอัตราการรอดชีพในผู้ป่วยเด็กกลุ่ม acute lymphoblastic leukemia ที่มีภาวะ hyperleukocytosis เมื่อเทียบกับไม่มีภาวะ hyperleukocytosis คิดเป็นร้อยละ 37.2 ต่อ 67.8 (p *value* < 0.0001) ซึ่งจะเห็นว่าอัตราการรอดชีพจากงานวิจัยนี้ซึ่งเก็บข้อมูลในประเทศไทยต่ำกว่าข้อมูลที่เก็บในต่างประเทศ และโรงพยาบาลอุดรธานียังไม่เคยมีการเก็บรวบรวมข้อมูลผู้ป่วยมาก่อน จึงเป็นที่มาของงานวิจัยชิ้นนี้

วัตถุประสงค์: อัตราการรอดชีพของผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันชนิดลิมฟอยด์ที่มีภาวะเม็ดเลือดขาวสูงมากผิดปกติ (hyperleukocytosis) ในผู้ป่วยเด็กโรงพยาบาลอุดรธานี

วิธีการศึกษา: การวิจัยนี้เป็นการศึกษาแบบ retrospective cohort study โดยรวบรวมข้อมูล ผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันชนิดลิมฟอยด์ที่มีภาวะเม็ดเลือดขาวสูงมากผิดปกติ (hyperleukocytosis) ในผู้ป่วยเด็ก ที่เข้ารับการวินิจฉัยและรักษาด้วยยาเคมีบำบัด ที่โรงพยาบาลอุดรธานี ตั้งแต่เดือนกรกฎาคม พ.ศ. 2553 ถึง เดือนพฤศจิกายน 2562 โดยใช้ฐานข้อมูลเวชระเบียน โรงพยาบาลอุดรธานี

ผลการศึกษา: งานวิจัยนี้เก็บข้อมูลผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันชนิดลิมฟอยด์ที่มีภาวะเม็ดเลือดขาวสูงมากผิดปกติ (hyperleukocytosis) ในผู้ป่วยเด็กทั้งสิ้น 22 ราย ผู้ป่วยมีอายุในขณะที่วินิจฉัยเฉลี่ย 6.3 ปี (0.3 – 14 ปี) ส่วนใหญ่เป็นเพศชาย คิดเป็นร้อยละ 59 ส่วนใหญ่เป็นชนิด B-ALL คิดเป็นร้อยละ 64 อาการและอาการแสดงที่พบมากที่สุดคืออาการตับม้ามโตโดยพบร้อยละ 95.5 รองลงมาคืออาการไข้และอาการเลือดออกผิดปกติ

คิดเป็นร้อยละ 81.8 และ 54.5 ตามลำดับ ผลเลือดขณะวินิจฉัย พบว่าจำนวนเม็ดเลือดขาวเฉลี่ยคือ 210,000 cells/cu.mm. (±247,683.7) ความเข้มข้นของเม็ดเลือดแดง (hemoglobin) 6.6 g/dL (±2.7) จำนวนเกล็ดเลือด 29,318 /cu.mm. (±17,038.8) ค่า lactate dehydrogenase 5,869 U/dL (±4,579.2) ภาวะแทรกซ้อนที่สามารถพบได้บ่อยในระยะเริ่มแรกของการรักษา คือ tumor lysis syndrome คิดเป็นร้อยละ 31.8 ผู้ป่วยมีอัตราการรอดชีพที่ 5 ปี อยู่ที่ร้อยละ 68.2 โดยไม่พบว่ามีปัจจัยที่สัมพันธ์กับอัตราการรอดชีพอย่างมีนัยสำคัญทางสถิติ ไม่ว่าจะเป็น ช่วงอายุ เพศ จำนวนเม็ดเลือดขาว ชนิดของมะเร็งเม็ดเลือดขาว

สรุป: จากผลการวิจัยพบว่าผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดเฉียบพลันที่ชนิดลิมฟอยด์มีภาวะเม็ดเลือดขาวสูงมากผิดปกติ (hyperleukocytosis) ในผู้ป่วยเด็ก มีอัตราการรอดชีพที่ 5 ปีอยู่ที่ร้อยละ 68.2 โดยไม่พบว่ามีปัจจัยที่สัมพันธ์กับอัตราการรอดชีพอย่างมีนัยสำคัญทางสถิติ ไม่ว่าจะเป็น ช่วงอายุ เพศ จำนวนเม็ดเลือดขาว ชนิดของมะเร็งเม็ดเลือดขาว

คำสำคัญ: ผู้ป่วยเด็กมะเร็งเม็ดเลือดขาวชนิดเฉียบพลัน, อัตราการรอดชีพภาวะเม็ดเลือดขาวสูงมากผิดปกติ, โรงพยาบาลอุดรธานี

Survival rate of pediatric acute lymphoblastic leukemia patients with hyperleukocytosis at Udon Thani Hospital

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Abstract

Background: Leukemia represents the most prevalent form of cancer in the pediatric population. The majority of affected children achieve favorable outcomes with standard treatment regimens, with high cure rates. However, the presence of hyperleukocytosis at initial presentation has been associated with increased risks of early complications and mortality. Data from studies conducted in developed countries indicated that the cure rate for pediatric patients with acute lymphoblastic leukemia (ALL) and hyperleukocytosis was approximately 64.5%. In contrast, a study conducted by the Faculty of Medicine at Prince of Songkla University reported a significantly lower overall survival rate among pediatric ALL patients with hyperleukocytosis compared to those without this condition, at 37.2% versus 67.8%, respectively (p value < 0.0001). These findings highlight a disparity in outcomes between patients in Thailand and those in more developed healthcare settings. Notably, this is the first collected report at Udon Thani Hospital, thereby providing the rationale for the present study.

Objective: To determine the survival rate of pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) presenting with hyperleukocytosis at Udon Thani Hospital.

Methods: This study employed a retrospective design. Data were collected from medical records of pediatric patients diagnosed with acute lymphoblastic leukemia accompanied by hyperleukocytosis who received chemotherapy at Udon Thani Hospital between July 2010 and November 2019. Patient information was retrieved from the hospital's electronic medical record database, including demographic, clinical, and laboratory findings.

Results: This study included a total of 22 pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) presenting with hyperleukocytosis at Udon Thani Hospital. The mean age at diagnosis was 6.3 years old (range: 0.3–14 years), with a male predominance (59%). The majority of cases were classified as B-ALL (64%). The most common clinical manifestation was hepatosplenomegaly, observed in 95.5% of patients, followed by fever (81.8%) and abnormal bleeding (54.5%). At diagnosis, the mean white blood cell count was

210,000 cells/cu.mm. (±247,683.7), mean hemoglobin level was 6.6 g/dL (±2.7), mean platelet count was 29,318 /cu.mm. (±17,038.8), and mean lactate dehydrogenase (LDH) level was 5,869 U/dL (±4,579.2).

The most frequently observed early treatment-related complication was tumor lysis syndrome, occurring in 31.8% of patients. The five-year overall survival rate was 68.2%. No statistically significant associations were identified between overall survival and factors such as age at diagnosis, sex, white blood cell count, or leukemia subtype.

Conclusion: The findings indicated that pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis treated at Udon Thani Hospital had a five-year survival rate of 68.2**.** No statistically significant prognostic factors were found to be associated with survival outcomes.

Keywords: Pediatric acute lymphoblastic leukemia, survival rate, hyperleukocytosis, Udon Thani Hospital

Introduction

Leukemia is the most common type of cancer in the pediatric population. In the United States, approximately 3,000 new cases of childhood leukemia are diagnosed annually.[1] In Thailand, an estimated 950 new cases are reported each year, accounting for 25–35% of all pediatric cancer cases.[2] With appropriate and standardized treatment, the prognosis for pediatric leukemia can be favorable. Data collected by the Thai Pediatric Oncology Group between 2015 and 2019 revealed a five-year survival rate of 81.7% for acute lymphoblastic leukemia (ALL).[2] However, prognosis significantly worsens in the presence of hyperleukocytosis.[3]

Hyperleukocytosis is defined as a white blood cell count exceeding 100,000/μL and is considered a hematologic emergency. It is associated with a range of potentially life-threatening complications, including tumor lysis syndrome and leukostasis, and contributes to a higher risk of early morbidity and mortality. These complications may manifest as central nervous system events (e.g., intracranial hemorrhage) or respiratory failure. Hyperleukocytosis is a recognized prognostic factor associated with adverse outcomes in pediatric leukemia. In children with ALL, the incidence of hyperleukocytosis ranges from 10.2% to 19.2%,[4-12] whereas in those with AML, it ranges from 12.6% to 21.7%.[4-6] Despite these challenges, advances in chemotherapy and supportive care over the past two decades have led to improved survival rates. Among pediatric ALL patients with hyperleukocytosis, five-year survival rates have been reported at 82.6%.[8] In contrast, AML patients with hyperleukocytosis have a five-year survival rate of 37.4%, primarily due to early complications such as leukostasis and disseminated intravascular coagulation (DIC).[13-19]

A study conducted by the Faculty of Medicine, Prince of Songkla University, examined pediatric patients diagnosed with acute leukemia and presenting with hyperleukocytosis between January 1998 and December 2017. The results demonstrated a significantly lower survival rate among patients with ALL who had hyperleukocytosis compared to those without the condition—37.2% versus 67.8%, respectively (p value < 0.0001). The cohort included 80 patients with hyperleukocytosis and 403 patients without. Identified factors associated with poorer survival outcomes included age less than 1 year or greater than 10 years, male sex, and an extreme white blood cell count exceeding 200,000 cells/cu.mm. (termed *extremely hyperleukocytosis*).[3] These findings highlighted that survival rates observed in this Thai cohort were lower than those reported in studies from developed countries. Notably, Udon Thani Hospital has undertaken a guideline by the Thai Pediatric Oncology Group. Therefore, the present study was initiated to assess survival rates and explore

prognostic factors influencing outcomes among pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis treated at Udon Thani Hospital.

Objectives

Primary Objective:

To determine the survival rate of pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) presenting with hyperleukocytosis at Udon Thani Hospital.

Secondary Objectives:

- To identify factors associated with survival outcomes in pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis at Udon Thani Hospital.
- To describe the presenting symptoms, clinical signs, and early treatment-related complications in this patient population.

Methodology

This study employed a retrospective cohort design. Data were collected from the medical records of pediatric patients diagnosed with ALL presenting with hyperleukocytosis who received chemotherapy at Udon Thani Hospital between July 2010 and November 2019 based on Pediatic Oncology Division's initiation. The data were retrieved from the hospital's electronic medical record system. The sample size was calculated based on a study conducted by the Faculty of Medicine, Prince of Songkla University (2023), which reported a hazard ratio of 2.04 for pediatric patients with acute leukemia and hyperleukocytosis. Using a two-sided test with a significance level (α) of 0.05 and a statistical power ($1-\beta$) of 0.80, the required sample size was determined to be 62 patients. An additional 10% was added to account for incomplete or missing data, resulting in a final target sample size of 69 patients.

Data collection was conducted retrospectively and categorized into three main domains: 1) demographic and baseline information, 2) disease characteristics, and 3) treatment-related data as therapeutic interventions and chemotherapy protocols. All collected data were verified for accuracy and recorded using statistical software for analysis. Descriptive statistics were used to summarize the baseline characteristics of the study population. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, the Independent t-test was used when the data were normally

distributed, and the Mann-Whitney U test was applied when the distribution was non-normal. The Kaplan-Meier method was used to estimate median survival time. The log-rank test was employed to compare survival curves between groups. In addition, Cox proportional hazards regression analysis was performed to identify factors associated with survival outcomes. This study was approved by the Human Research Ethics Committee of Udon Thani Hospital on December 16, 2024 (Reference No. 175/2567).

Results

This retrospective study included pediatric patients diagnosed with ALL presenting with hyperleukocytosis who received chemotherapy at Udon Thani Hospital over a 9-year period, from July 2010 to November 2019. A total of 22 patients met the inclusion criteria. The mean age at diagnosis was 6.35 years old (range: 0.33–14 years), with the majority of patients (63.6%, n = 14) aged between 1 and 9 years. Most patients were male (59%, n = 13). The predominant leukemia subtype was B-cell ALL, observed in 64% (n = 14) of patients. Approximately one-quarter of the cohort had abnormal cytogenetic findings, with roughly half of the patients successfully undergoing cytogenetic chromosome analysis (Table 1).

The most common clinical presentation was hepatosplenomegaly, observed in 95.5% of patients (n = 21), followed by fever in 81.8% (n = 18) and abnormal bleeding in 54.5% (n = 12) (Table 2).

At diagnosis, the mean white blood cell count was 210,000 cells/cu.mm. (±247,683.7), mean hemoglobin level was 6.63 g/dL (±2.7), mean platelet count was 29,318 /cu.mm. (±17,038.8), and mean lactate dehydrogenase (LDH) level was 5,869 U/dL (±4,579.2) (Table 3).

Early treatment-related complications included septic shock in 22.7% of patients (n = 5), tumor lysis syndrome at diagnosis in 18.2% (n = 4), and hyperglycemia also in 18.2% (n = 4). Additionally, tumor lysis syndrome occurred in three more patients after initiation of chemotherapy, bringing the total incidence to 31.8% (n = 7), making it the most frequently observed complication (Table 4).

Table 1 General characteristics of pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis at Udon Thani Hospital

Characteristic	**n (%)**
Age (year), mean (±SD)	6.3 (±4.9)
Age group (years)	
- 0 – 1 years	2 (9.1)
- 1 – 9 years	14 (63.6)
- 10 – 15 years	6 (27.3)
Gender	
- Male	13 (59)
- Female	9 (41)
Immunophenotyping	
1. B-ALL	14 (64)
2. T-ALL	3 (13.5)
3. Diagnosis based on morphology (due to emergency conditions and limitations in laboratory testing)	4 (18)
4. Results unreadable due to specimen issues	1 (4.5)
Chromosome	
1. Normal chromosome	6 (27.3)
2. Abnormal chromosome	5 (22.7)
3. Not performed due to emergency conditions and limitations in laboratory testing	4 (18.2)
4. Results unreadable due to specimen issues	7 (31.8)

Remark: B-ALL is typically characterized by the presence of markers like CD19, CD20, and CD22, while T-ALL is identified by markers like cytoplasmic CD3, CD2, CD4, CD5, CD7, and CD8

Table 2 Symptoms and clinical signs of patients

Symptoms and clinical signs	**n (%)**
Hepatosplenomegaly	21 (95.5)
Fever	18 (81.8)
Bleeding (grade 3, 4)	12 (54.5)
Lymphadenopathy	10 (45.5)
Bone pain	4 (18.2)
CNS metastasis	0 (0)

Table 3 Blood parameters of patients with acute leukemia and hyperleukocytosis

Blood parameters	**ALL** **mean (±SD)**
White blood cell count (cells/cu.mm.)	210,355 (±247,683.7)
Hemoglobin (g/dL)	6.63 (±2.7)
Platelet count (/cu.mm.)	29,318 (±17,038.8)
Lactate dehydroginase (U/dL)	5,869 (±4,579.2) (n=10)

Table 4 Early treatment complications in patients

Early treatment complications in patients	**ALL** **n (%)**
Tumor lysis syndrome at diagnosis	4 (18.2)
Clinical Tumor lysis syndrome after treatment	3 (13.6)
Internal organ bleeding (GI bleeding)	1 (4.5)
Clinical leukostatis	1 (4.5)
Severe infection	
-Septic shock	5 (22.7)
-Pneumonia	3 (13.6)
-Disseminated abcess (liver and splenic)	2 (9.1)
Respiratory failure	3 (13.6)

Early treatment complications in patients	ALL n (%)
Other complication	
1. PRES	1 (4.5)
2. Spontaneous pneumothorax	1 (4.5)
3. Pancreatitis	1 (4.5)
4. Chemical subarachnoiditis	1 (4.5)
5. Hyperglycemia	4 (18.2)
6. Mucositis grade 4	2 (9.1)

The findings of this study indicated that pediatric patients with ALL and hyperleukocytosis had a 5-year survival rate of 68.2% (Figure 1). No statistically significant factors were identified as being associated with survival rates, including age group, gender, white blood cell count, or type of leukemia (Table 5).

The analysis of data regarding treatment protocols revealed that patients receiving the high-risk protocol had a significantly higher survival rate compared to those treated with the very high-risk protocol, with a p value of 0.0306 (Figure 2). Furthermore, there was no statistically significant difference in survival rates between patients who received blood exchange transfusions and those who did not, with a p value of 0.8056 (Figure 3).

Table 5 Multivariate analysis of risk factors associated with overall survival in pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis

Risk factor	Hazard ratio	95% CI	p value
Age			
- < 1 year	2.834	0.291-27.550	0.369
- 1-9 year	1.000		
- ≥10 year	2.894	0.58-14.434	0.195
Sex			
- Male	6.211	0.746-51.706	0.091

Risk factor	Hazard ratio	95% CI	p value
- Female	1.000		
White blood cell counts			
- <200,000 cell/cu.mm.	1.000		
- ≥200,000 cells/cu.mm.	1.709	0.381-7.667	0.484
Immunophenotyping			
- B -ALL	0.698	0.072-6.726	0.756
- T-ALL	1.000		
- NA	2.242	0.233-21.61	0.485

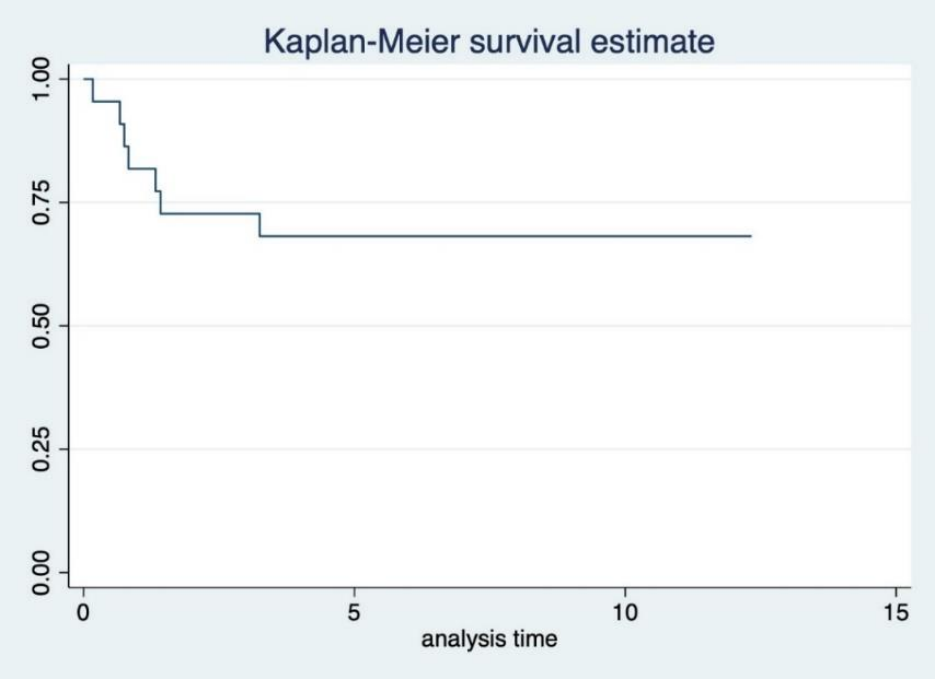

Figure 1 Overall survival rate of pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis

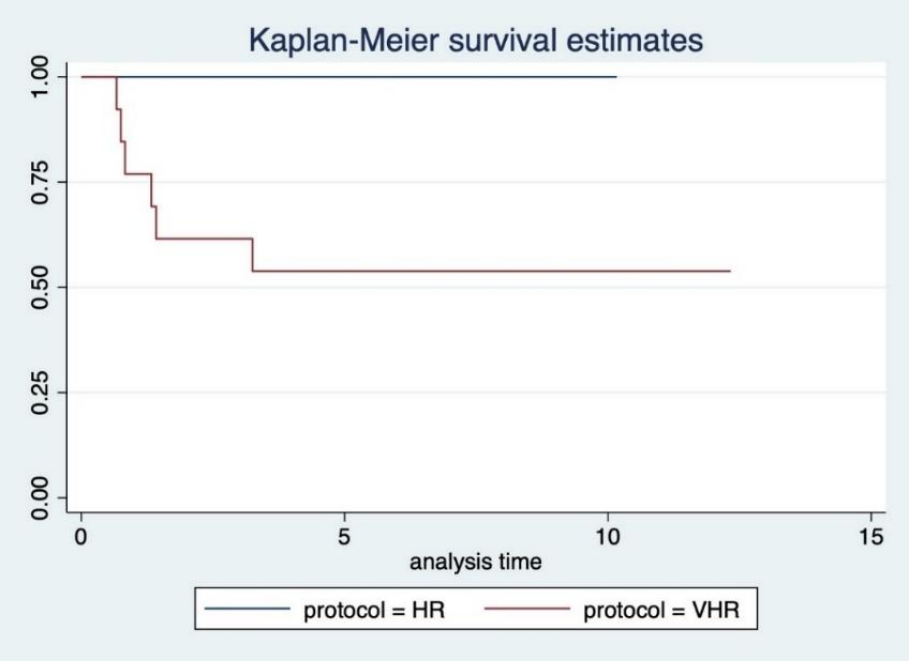

Figure 2 Overall survival rate of pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis receiving Thai POG ALL high-risk protocol versus very high-risk protocol following the induction phase (p value 0.0306)

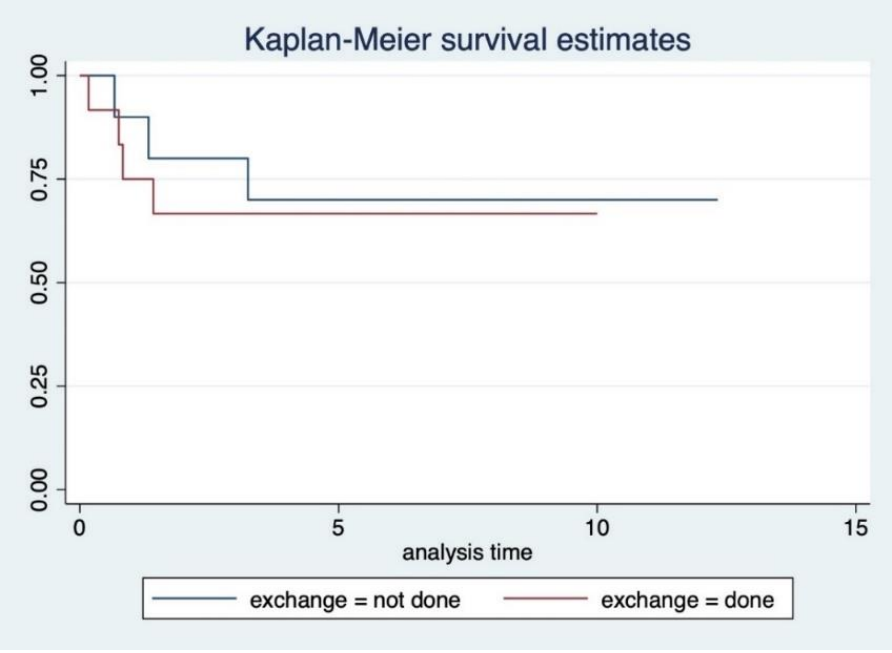

Figure 3 Overall survival rate of pediatric patients with acute lymphoblastic leukemia and hyperleukocytosis who underwent exchange transfusion versus those who did not (p value 0.8056)

The small sample size (n = 22) was a major limitation and should be explicitly acknowledged. The limited statistical power due to the small sample size might explain why no statistically significant factors were identified in the multivariate analysis.

Discussion

This retrospective study examined pediatric patients with acute lymphoblastic leukemia (ALL) and hyperleukocytosis treated at Udon Thani Hospital over a nine-year period. Among 244 children diagnosed with ALL during the study period, 22 patients (9%) was the most important limitation, presented with hyperleukocytosis, a proportion consistent with previous international reports, which had reported incidence rates ranging from 10.2% to 19.2% among pediatric ALL patients.[4-12] A 9% patient presentation rate of hyperleukocytosis (WBC > 100,000/microliter) had significant implications for patient management, particularly in the context of leukemia. It indicated a higher-than-expected occurrence of this condition, potentially leading to increased risks of complications like leukostasis, tumor lysis syndrome, and disseminated intravascular coagulation. This finding also suggested a need for more aggressive and potentially specialized treatment approaches, including cytoreduction techniques like leukapheresis, to reduce the risk of adverse outcomes. The five-year overall survival (OS) rate in this cohort was 68.8%, which was notably higher than the 37.2% reported by the Faculty of Medicine at Prince of Songkla University[3], yet lower than the 82.6% reported in studies from developed countries.[8]

Previous research had identified several poor prognostic indicators in ALL with hyperleukocytosis, including age under one year, white blood cell counts $\geq$200,000 cells/cu.mm., and T-lymphoblastic immunophenotype, all of which had been significantly associated with reduced survival.[3] However, this study did not find these factors to be statistically significant predictors of survival, suggesting potential differences in population characteristics or sample size limitations.

With regard to treatment protocols, all patients who died in this cohort had received the Thai Pediatric Oncology Group (Thai POG) "very high risk" protocol. This observation might reflect the increased treatment intensity and associated risk of infection in this group. Conversely, patients receiving the "high risk" protocol were more likely to have been treated in later years, when supportive care measures had improved in infection control, management of tumor lysis syndrome, or nutritional support—potentially contributing to better

outcomes. These factors might have influenced the survival advantage seen in the high-risk protocol group (p value 0.0306).

In this study, the use of exchange transfusion as an intervention for hyperleukocytosis was not associated with a statistically significant difference in overall survival (p value 0.8056). While some studies had advocated for leukoreduction strategies, such as exchange transfusion, to reduce early mortality and improve survival,[19] other literature recommended individualized decision-making based on the patient's clinical condition.

Overall, these findings emphasized the need for further prospective studies with larger sample sizes to better delineate prognostic factors and optimize treatment strategies for pediatric patients with ALL and hyperleukocytosis. Further research involving a larger cohort emphasized the clinical implication potentially through extended data collection periods or multicenter collaboration is recommended to more accurately identify prognostic factors and validate these outcomes, as well as focusing on further improving survival rates, reducing treatment-related toxicities, and addressing disparities in access to care.

Conclusion

Pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) and concurrent hyperleukocytosis had a five-year overall survival rate of 68.2%. No statistically significant associations were found between overall survival and clinical variables or leukemia subtype.

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